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MASSIVE HEMATEMESIS*

ANALYSIS OF 300 CONSECUTIVE CASES

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ONE COULD NOT JUSTIFIABLY UNDERTAKE to discuss the topic of massive hematemesis without reference to much in the vast library of reports on this subject but because of its extensiveness a thorough review cannot here be presented. Adequate reports have been made by Gray and Sharpe,[1] Zinninger,[2] Meulengracht,[3] Heuer,[4] Meyer,[5] Eads,[6] Allen and Benedict,[7] Hinton,[8, 9] Balfour,[10] Jordan and Kiefer,[11] and a host of others. In seeking, however, to learn the best methods for management of this grave condition, one encounters a divergence of opinions among authors as to whether treatment should be medical or surgical and if the latter, how such cases are to be selected. Other problems in therapy include those concerning the advisability of using gastric siphonage, oral feeding, blood transfusions, and sedation.

In order to arrive at a better understanding of the principles of anatomy, physiology, and pathology involved and to correlate these principles with a plan of rational therapy, a study was undertaken at the St. Louis City Hospital.

In this study, 300 patients who had presented the symptoms of massive and severe hematemesis were selected. No patient was included in this study who had not vomited large quantities of gross blood and who did not show evidence of blood loss by shock or by severe anemia or by both. Thus, individuals who may have vomited as much as a cupful of blood, but who did not show evidence of shock or severe anemia, were omitted. A second portion of this project was begun early in 1946 and consisted of treatment of those patients presenting massive hematemesis according to a modified plan. The results in this series of 73 patients have also been determined.

CAUSES

In our series of 300 patients (Fig. 1), chronic duodenal ulcer leads the list of causes, accounting for 171 patients or 57%. No diagnosis was made in four patients (1.3%). Acute gastritis was the underlying cause of massive hematemesis in 42 patients (14%) while chronic gastric ulcer accounted for 33 patients (11%). Ruptured esophageal varix occurred in 24 patients (8%) and

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chronic gastritis in 12 patients (4%). Gastric carcinoma was one of the rarer causes of massive hematemesis accounting for only four such cases (1.3%). Marginal ulcer occurred in four patients (1.3%), Curling ulcer in two patients (.6%) and carcinoma of the esophagus in three patients (1%) while trauma of a bullet wound was the cause in one patient (.3%).

SEX AND AGE INCIDENCE

Two hundred and forty-seven of the patients (82%) were males while only 53 patients (18%) were females (Fig. 2). The incidence of massive hema-

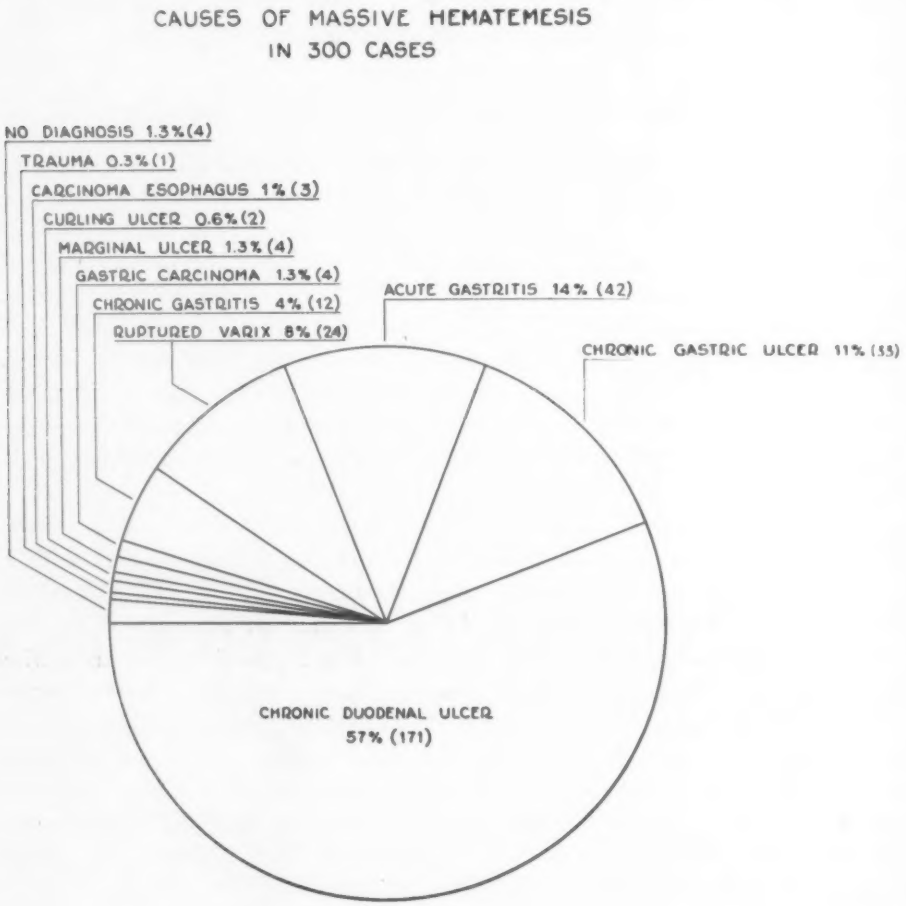

FIG. 1

temesis was greater between the fourth and eighth decades in both sexes, the highest incidence occurring in the sixth decade (23% of the males).

MORTALITY IN PATIENTS TREATED BY CUSTOMARY MEASURES

The overall mortality rate in 300 cases was 25%. Consistent with observations and reports of others studying this subject, mortality rate was found to

increase in those who had reached or passed the fifth decade of life. Thus it was seen that among males, while in the fourth decade, only 10% died, 20% died in the fifth decade, 28% in the sixth, and 38% in the seventh (Fig. 3). Certain pathologic lesions bore a higher mortality incidence than others (Fig. 4). Thus of four patients who bled massively from carcinoma of the stomach, all died. The two patients with Curling ulcers, both died, and three patients of the four who presented marginal ulcers died. Of the 24 patients with ruptured esophageal varices, 71% died and in those patients who bled from carcinoma

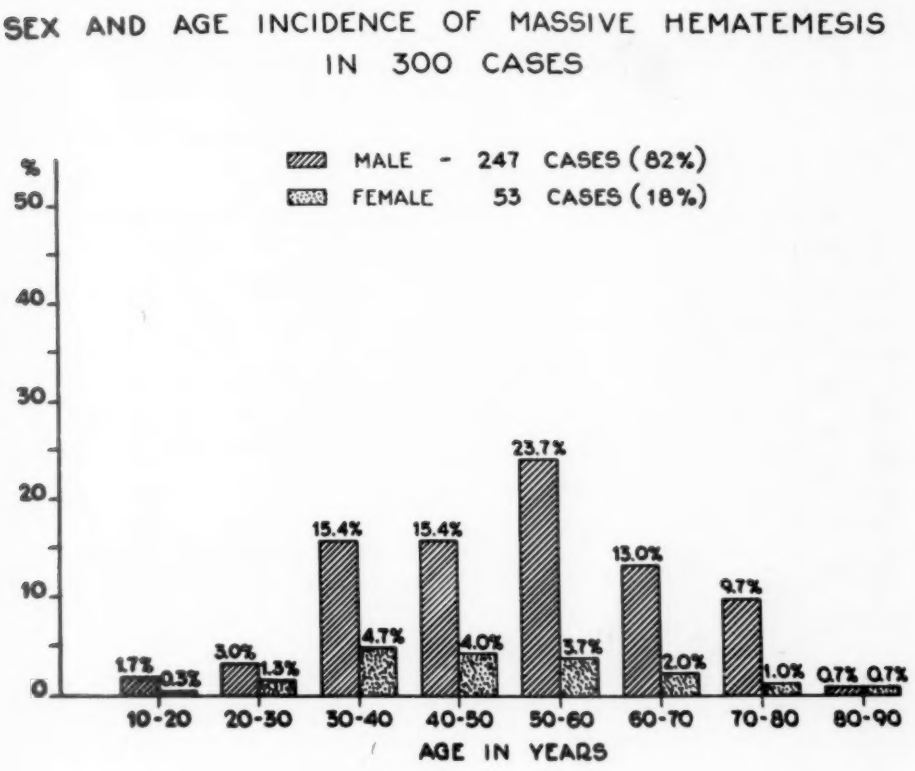

FIG. 2

of the esophagus, 66% died. Of 33 chronic gastric ulcer patients, deaths ensued in 48%, while in those with chronic duodenal ulcer only 13% died. In patients who presented acute gastritis (42) only 12% died, and of those who presented chronic gastritis as the basis of massive hemorrhage (12) 9% died.

PATHOLOGY

Surgical or autopsy examination afforded opportunity for pathological examination in about 85% of those patients who died. Of particular interest and significance was the status of the eroded blood vessel. As is well known, the commonest vessels involved in such major upper intestinal hemorrhages are the branches of the right and left gastric and the pancreatico-duodenal

arteries and the esophageal veins. The size of vessels involved varied from large and prominent gastric arteries to those involved in multiple superficial gastric ulcers which could not positively be identified. In one instance erosion of a chronic gastric ulcer had extended into liver sinusoids.

Sections of arteries and veins involved were not obtained in all instances. However, in those who died with erosion of a large, easily demonstrable artery (usually in the base of a chronic ulcer) microscopic studies were usually performed. In nearly all of these sections there was seen and described a partial

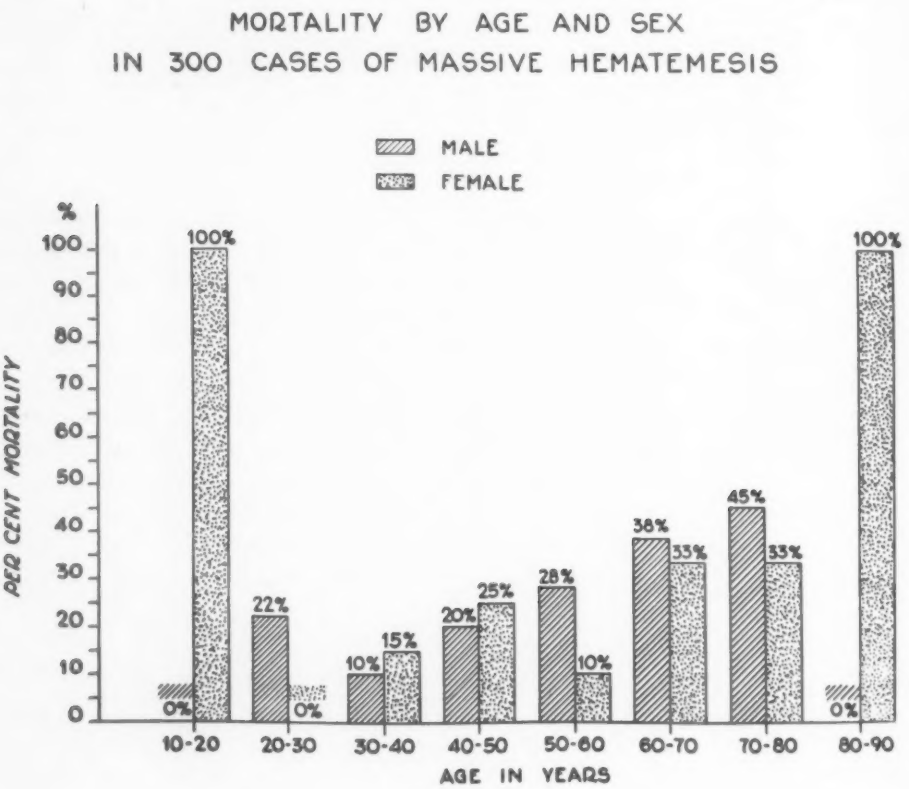

FIG. 3

or complete block of the eroded wall by antemortem thrombus, and in these the stomach and duodenum contained little or no fresh blood. This demonstration of thrombus formation in even large eroded gastric arteries is of paramount importance in arriving at a rational plan of therapy. It is evident that many of these patients did not die, as has been commonly assumed, from acute exsanguination through a wide open artery. This misconception has led to recommendations that patients with arteriosclerosis and chronic ulcers should be subjected more promptly to operative closure of the bleeding point. It would rather appear on the basis of pathologic studies that just the contrary is true, for thrombus has often already formed prior to the time of death and such a

death, therefore, must be attributed not to continued acute hemorrhage but rather to the complications of diminished blood volume (shock, cardiac failure, anemia, pneumonia, *etc.*) produced after the hemorrhage had ceased. This fact is confirmed by the clinical course of patients who died. They did not die in a matter of minutes or hours (with one exception) as would be expected from a persistent fulminant hemorrhage, but died from two days to three weeks after the onset of bleeding. Of the 75 patients who died, 71 of them did not receive even a moderate fraction of blood which would have been required to replace the amount lost.

On this evidence then one must logically reason that therapy should primarily be directed not toward surgical closure of the injured vessel which natural processes often will close spontaneously, but toward support of the depleted blood volume.

PHYSIOLOGY

The body response to massive blood loss is well known. In an attempt to supply vital centers with the remaining blood volume there is a generalized vasoconstriction, an increased rate of heart action, and absorption of tissue fluids into the general circulation. If inadequate blood volume continues, anoxia with its irreversible tissue damage ensues. In view of the universal acceptance of this well-established fact, it is surprising to find recommendations still made that in such a situation blood should not be used or if used, should be used sparingly. The theory that restoring blood pressure risks "blowing out" a forming thrombus has no scientific substantiation while on the other hand, no one has yet been able to improve on shock-prevention as the best shock-therapy. To wait for a fall of blood pressure to 80 or 100 mm. of mercury before administering a "small transfusion" as is often recommended is a direct contradiction of sound physiologic principles.

BLOOD REPLACEMENT PLAN

If these pathologic facts and physiologic principles are correct, the optimal choice of treatment in massive hematemesis should be essentially replacement of as much blood as has been lost as promptly as possible until thrombus formation has sealed the eroded vessel or vessels. In testing these principles during the past two years, 73 patients were treated by adequate and prompt blood replacement. The distribution of these 73 patients by sex and age corresponds closely to that of the previous group studied. There were for example 51 of these 73 patients who had reached or passed the fifth decade of life, and there were eight of these who had reached or passed the eighth decade of life. Operative interference during active bleeding was not undertaken in any of these cases. Feedings were usually administered, and the type of feeding varied between the Meulengracht diet, the Sippy diet, liquid diet, and protein-dextrimaltose ("pre-digested") liquids. As should be anticipated, the difference in mortality rate was striking (Fig. 5). Only 4% of this group of 73 patients died as compared to 25% of the 300 treated by various methods.

In further analyzing this difference in mortality, it is clear that the single most important factor in minimizing death has been that of adequate blood replacement. It is highly doubtful if this policy could be routinely used in an institution which does not have a blood bank facility. The total quantity of blood required by many of these patients is enormous as judged by transfusion standards of a decade ago. Often patients who had lost large quantities of blood and who were still bleeding when admitted to the hospital received as much as three and four liters of blood during the first 24-hour hospital period. The frequent use of intravenous saline solution should be condemned as it does nothing toward re-establishing blood volume, and encourages pulmonary edema. The fluid of most value to be used while blood is being cross-matched

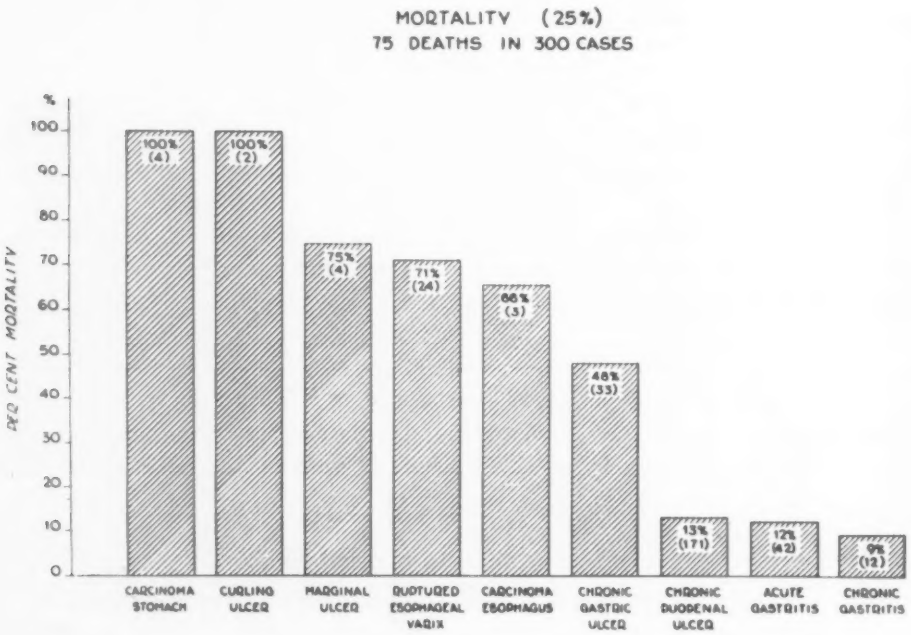

FIG. 4

is plasma. Another essential for enforcing adequate blood replacement is the readily available facility for rapid determination of blood requirements. The need for blood cannot properly be determined by a patient's general appearance, pulse, or blood pressure. The older methods of blood study such as blood count and hematocrit are either undependable or too *time consuming* to be of value in these cases. The most desirable method for accurately following blood volume changes is the copper sulfate falling drop method.[12] The device for this simple procedure has been set up on the hospital divisions and in the matter of a few minutes with only a few drops of blood, the initiated houseofficer is able to discover the specific gravities of blood and plasma, the hemoglobin, and the hematocrit.

In addition to blood volume replenishment, several other factors have been given special attention.

1) Gastric siphonage
2) Diet and antacid therapy
3) Sedation
4) Surgery
5) Early differential diagnosis.

1) *Gastric Siphonage.* The insertion of a Levine tube via the esophagus into the stomach was seen to produce fatal hemorrhage in two patients. It was instrumental in provoking increased hemorrhage in several others. Ice water for lavaging was used in the two cases of fatality, and one of these

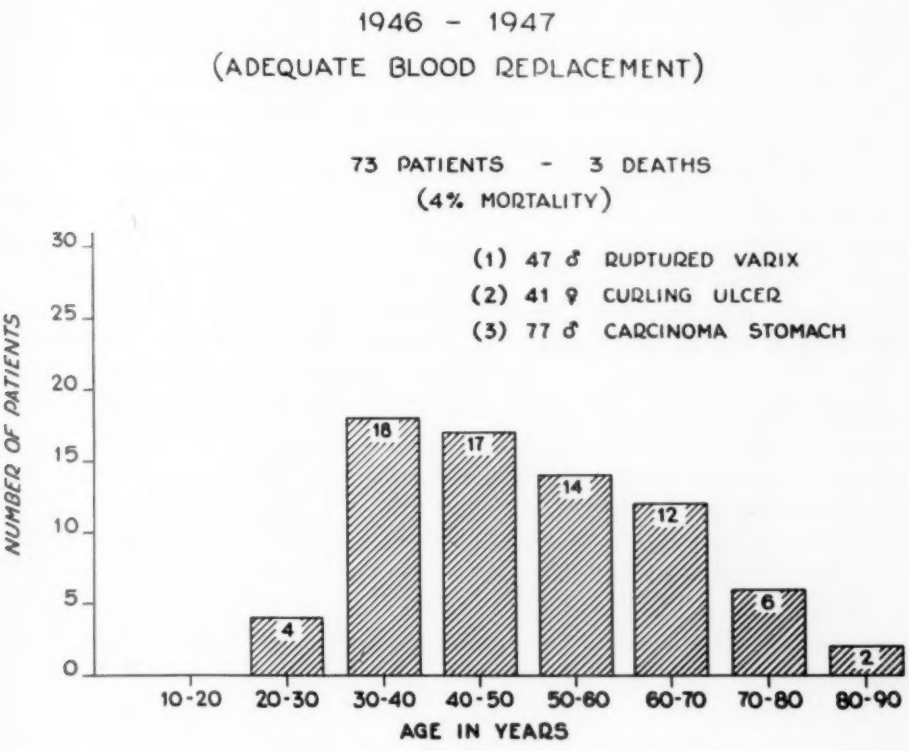

FIG. 5

patients expired while the process was being carried out. The danger of traumatizing a varix or ulcer should interdict use of the tube unless there is definite gastric distention and nausea.

2) *Diet and Antacid Therapy.* The question as to whether feeding should or should not be employed has long been debated. Meulengracht has reported favorably on feeding pureed diets although a large proportion of his ulcer patients presented only minor bleeding. In the light of current knowledge that most of these patients have a deficit of protein and vitamin which impedes

tissue repair, it becomes imperative that they receive large amounts of readily assimilable protein, carbohydrate, and vitamin. The most satisfactory method for administering these essentials we have found has been oral ingestion of 200 cc. every two hours of the following preparation:

Predigested protein powder (polypeptide)	150 Gm.
Dextri-maltose	300 Gm.
Vitamin C (cevitamic acid)	1 Gm.
Liquid multiple vitamin	1 cc.*
Water q.s.	2400 cc.

This preparation is well tolerated with rare exception and serves not only the purpose of supplying greatly needed nutriment but also produces symptomatic relief of ulcer pain. This is apparently accomplished through the protein antacid effect which is much more effective in degree and in duration than the more commonly employed antacid powders. This same preparation has been highly satisfactory in relieving severe ulcer pain of impending perforations. The polypeptide component is used rather than amino acids since it is palatable.

3) *Sedation.* The most generally adopted plan for sedation in the past has been that of administering morphine or barbiturate as needed. In practice this usually degenerates to a matter of a sedative being finally given after the patient has repeatedly complained to the nurse of restlessness, fear, or pain. The numerous psychogenic impulses attendant upon massive hemorrhage and nausea have appeared often to provoke further active bleeding and it has, therefore, been our policy to relieve these patients totally of their adverse stimuli. This has been accomplished by administering a single initial dose of morphine followed by hypodermic injections of two grains of sodium phenobarbital every two hours as needed to keep the patient drowsy. We have considered the patient properly sedated when it is necessary physically to arouse him in order to obtain replies to questions. The danger of oversedation must, of course, be carefully avoided.

4) *Surgery.* The major disadvantages to surgical procedure during active bleeding are: a) Patients are in poor condition from blood loss and while bleeding is active they may be expected to become worse.

b) Nutritional deficiencies of a chronic nature must be anticipated in patients whose ulcers are active enough to have produced erosions of major vessels. Operations undertaken before these deficiencies have been corrected must result poorly in many cases.

c) The nature and location of the ulcerative lesion cannot safely or accurately be determined early in the course of hemorrhage and routine operative approach with its risk cannot be serviceable or successful enough in treating all causes of massive hemorrhage to justify its use. As pointed out by Stone[14] such an operation may still fail to discover or relieve the trouble.

d) Finally, the ultimate test of value, that of clinical results in the non-

* Any liquid vitamin which contains the daily requirements should suffice. Upjohn's "Zymadrops" has become our material of choice.

surgical treatment of massive hemorrhage speaks unequivocally against operative interference. Prior to our initiation of this non-operative plan of therapy, ten patients had been operated upon late but while still bleeding and death ensued in 90%.

An interesting study in this regard is being conducted by Stewart[13] *et al.* They are combining massive blood replacement and exploratory laparotomy within the first 24 hours of hospitalization. Their results in such treatment of 19 patients have been accompanied by four deaths representing a mortality of 21% which may improve as the series of cases enlarges but which we doubt will ever compare favorably to active and complete non-surgical management.

A word should be said about that small group of patients who continue bleeding for seven to ten days or who begin bleeding again after apparent control. While the urge to intervene is great, the wisdom of persisting in the plan as set forth has been demonstrated conclusively in this series in that all patients finally ceased bleeding and were improved to the point that surgery could be undertaken without great risk. On the other hand, the inadvisability of operating on this type of patient is forcibly demonstrated by our extremely poor results of nine deaths in those ten patients so treated prior to our adopting the non-surgical plan.

5) *Early Differential Diagnosis.* The patient with active or recent major intestinal hemorrhage should not be subjected to enthusiastic diagnostic routines. Hemorrhage should be treated only symptomatically until controlled and then the matter of diagnosis may be pursued without the great danger of re-precipitating or exaggerating hemorrhage. In our own series of patients we have seen major hemorrhages re-started by barium studies and gastric analyses. The information so obtained rarely if ever alters the prescribed course of therapy early in the condition and so it becomes a matter of accomplishing an earlier diagnosis solely for the purpose of the record at the expense of increased mortality. It requires seven to ten days for moderately firm fibroblastic tissue reaction to form in an organizing thrombus and this picture should be borne in mind by the gastroscopist and fluoroscopist lest irreparable harm be done.

SUMMARY

Some of the results from a study of 300 patients with severe, massive hematemesis have been presented. The results of 73 patients treated by a massive blood replacement plan have also been presented. Mortality by this latter plan has been reduced to 4%. There was no death from chronic peptic ulcer, the commonest cause of massive hematemesis.

The following plan is, therefore, recommended for treatment of massive hematemesis during the actively bleeding stage:

1) Careful determination of blood needs by the copper sulfate falling drop method repeated frequently.
2) Complete restoration of blood as promptly as possible.

3) Oral administration of predigested protein-carbohydrate-vitamin mixture.
4) Adequate, continuous sedation.

The following procedures have been found to increase mortality during the actively bleeding stage:

1) Surgery
2) Indwelling stomach tube with constant suction
3) Gastric lavage
4) Active gastric diagnostic studies.

The problems in management of these patients after the active hemorrhage stage has passed have not been the province of discussion at this time, but instead, emphasis has been placed on the principles and factors of importance in the management during the stage of active hemorrhage. Following the control of hemorrhage and the restoration of nutrient and blood essentials, the advisability of elective surgical intervention may more easily be determined.

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THE MANAGEMENT OF BLEEDING DUODENAL ULCERS*†

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THE SURGEON FACES FEW THERAPEUTIC problems that are more perplexing than the management of a patient who has had a sudden, massive hemorrhage from a duodenal ulcer. It is a question of which course of action is most likely to lead to recovery, and when confronted with the individual case, statistics do not provide the answer. Reports have been difficult to interpret as authors have not always set down clearly their criteria for placing a patient in the severe hemorrhage group.

Recent publications by Heuer,[1] Gordon-Taylor,[2] and Hinton,[3] indicate that the present mortality rate without operation varies between 8 and 12 per cent in the United States and England, while Meulengracht[4] reports the death rate in Denmark, under his free feeding regime, as 2.5 per cent. These results are a distinct improvement over the mortality rate of 15 to 74 per cent reported much earlier by Gordon-Taylor,[5] Finsterer,[6] Chiesman,[7] Allen,[8] and others. The improvement in the nonoperative group appears to be due largely to the more generous use of blood transfusions.

Surgeons quite naturally have been interested in a direct attempt to stop bleeding by ligation of the bleeding vessel or vessels. This objective, as a rule, has been accomplished by gastric resection with excision of the ulcer and ligation of the vessels adjacent to the ulcer. In the past such a major procedure in a seriously ill patient usually carried a high mortality although Gordon-Taylor[9] in 1939 reported a series of 18 cases operated upon within 24 hours of the onset of bleeding with only one death, a mortality rate of 5 per cent, and Heuer[1] in 1946 reported a 10 per cent mortality in 21 cases operated upon at the New York Hospital. According to the same authors, operations performed 48 hours or longer after erosion of a large vessel resulted in a 50 to 70 per cent mortality rate.

These figures support the repeatedly stressed advice that, if surgery is to be carried out with a low mortality, the decision to operate must be made early. This decision is frequently a difficult one because during the first 48 hours there is no certain way by which the fatal type of hemorrhage can be differentiated from bleeding which will stop with nonoperative measures. Continuous recurrent, or sudden massive hemorrhage under a strict medical regime generally are accepted as the prime requisites for operation during the bleeding stage.

Mikulicz[10] reviewed the problem of treating bleeding duodenal ulcers 51

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years ago and came to the conclusion, as did Kronlein,[11] about 10 years later, that operation during the phase of active bleeding was extremely hazardous and that the patients stood a much better chance of survival if subjected to a conservative regimen.

It was Finsterer,[12, 13] who drew attention probably more emphatically than any other surgeon to the high mortality rate which followed late intervention in bleeding duodenal ulcers. After watching several deaths in young persons, he started his policy of operating at the end of 48 hours if the hemorrhage had not stopped. In his estimation, the third day was the critical period after which surgical intervention resulted in a disproportionately high mortality. In 1918 he started the first of a long series of contributions advocating early intervention with gastric resection and pyloric exclusion. In 1933 he[6] reported 46 cases operated upon early (within 48 hours) with a mortality rate of 4.3 per cent and a group of 55 patients operated upon after this interval with a mortality rate of 32.7 per cent. His enthusiasm for early intervention has been shared by Allen and Benedict[14] in so far as it pertained to the older age group.

While blood transfusions were used during these years, the blood was not administered in the generous amounts that were found beneficial in treating traumatic hemorrhage encountered in World War II. With adequate blood replacement, which is possible with a reliable blood bank, both the internist and the surgeon are allowed more time in which to plan a patient's therapeutic course and there is reason to believe that this factor alone will result in improved mortality figures for both the operative and nonoperative cases.

It is interesting to note that Gordon-Taylor,[2] who was one of Finsterer's early adherents, recently has changed his views about the urgency of immediate surgery. After making an intensive study of the disease in Great Britain, he has been impressed by the improvement in nonoperative measures now being employed and in his latest article arrives at the conclusion that "while Finsterer's third day may possibly be a critical period for operation the successful intervention at a later date in patients suffering from bleeding belie the universality of the dictum."

We have reviewed the records of 177 patients with severe bleeding from duodenal ulcers. The diagnosis was established by roentgenography, operation, or, in the fatal cases, by autopsy. The criteria of severe bleeding were a drop in hemoglobin to 65 per cent or less and a reduction in red cells to 3,500,000, or less. One hundred and eight of these patients had a hemoglobin of less than 50 per cent and a red count of less than 2,500,000.

In this series of 177 cases (Table I) there was a total of 11 deaths, a mortality rate of 6.2 per cent. One hundred and sixty-five patients were treated by nonoperative measures with seven fatalities, a mortality rate of 4.2 per cent. Twelve patients did not show a satisfactory response to conservative treatment and were operated upon while actively bleeding. All were operated upon in the late period, that is after more than 48 hours of rapid blood loss, and four died, a mortality rate of 33.3 per cent.

There were 93 patients under 50 years of age (Table II). Nine were treated by operation with three deaths, a mortality of 33.3 per cent, but there were no deaths in the group of 84 patients treated without operation.

There were 84 patients over 50 years old (Table III). Three were treated by operation with one death, a mortality of 33.3 per cent. Eighty-one were

TABLE I.—*Bleeding Duodenal Ulcers*

Treatment	Number of Patients	Deaths	Mortality %
Non-operative	165	7	4.2
Operative	12	4	33.3
Total	177	11	6.2

TABLE II.—*Bleeding Duodenal Ulcers*

Treatment	Under Age 50 Number of Patients	Deaths	Mortality %
Non-operative	84	0	0.0
Operative	9	3	33.3
Total	93	3	3.2

treated by nonoperative measures and seven of these died, a mortality of 8.6 per cent. Since there were no deaths among the patients under 50 years of age who were treated without operation, it would appear that age is a factor of some importance in estimating the chance of survival of a patient under conservative treatment.

TABLE III.—*Bleeding Duodenal Ulcers*

Treatment	Over Age 50 Number of Patients	Deaths	Mortality %
Non-operative	81	7	8.6
Operative	3	1	33.3
Total	84	8	9.5

Of the patients beyond 50 years of age who died of hemorrhage, the advent of the bleeding phase of the ulcer generally was accompanied by additional pathologic conditions which contributed materially to the ultimate demise. Arteriosclerosis appeared to be one of the most important contributary causes of death. (Table IV.)

A summary of the operative deaths is shown in Table V. Two of the four operative deaths appear to have been caused by pulmonary complications while the other two deaths were due to failure to control the bleeding

by operation; in one case a transduodenal suture of the bleeding ulcer was attempted and in the other the ulcer was not excised at the time of the gastric resection and continued to bleed.

TABLE IV.—*Bleeding Duodenal Ulcers*
Analysis of Non-operative Deaths

Sex	Age	Lowest HB	Lowest R. B. C.	Transfusions Whole Blood	Duration of Life After Bleeding Started	Comments
Male	60	38%	2.3 M	None	11 hours	Admitted to G. U. service with hydronephrosis, luetic aortitis, coronary sclerosis.
Male	73	45%	2.2 M	1000 cc	21 days	Slow blood loss. Bundle branch block. Senile dementia.
Male	80	32%	2.1 M	500 cc	13 hours	Cirrhosis of liver. Coronary sclerosis. Diabetes Mellitus. Senility.
Male	60	49%	2.5 M	500 cc	11 hours	Paresis, cerebrospinal syphilis. Death from cerebral embolus.
Male	63	18%	1.0 M	6200 cc	4 days	Posterior ulcer which did not penetrate into pancreas.
Male	65	46%	2.1 M	1000 cc	3 days	Sudden death without shock. Large substernal mass.
Female	50	41%	2.3 M	3600 cc	12 days	Marked arteriosclerosis. Died of cerebral hemorrhage with HB of 72%.

TABLE V.—*Bleeding Duodenal Ulcers*

		Analysis of Operative Deaths						
Sex	Age	Lowest HB	Lowest R.B.C.	Previous Bleeding Episodes	Duration of Pre-operative Bleeding	Transfusions Whole Blood	Type of Operation	Comment
Male	36	45%	2.6 M	1	3 days	2750 cc	Gastric resection	Death 48 hours after operation with temperature of 107 and pulmonary consolidation.
Male	38	54%	3.1 M	1	11 days	2000 cc	Gastric resection	Hiccoughs, pneumonia on 7th postoperative day.
Male	29	37%	2.0 M	3	4 days	2800 cc	Transduodenal suture	Death from hemorrhage 10th postoperative day.
Male	67	42%	2.1 M	4	4 days	5500 cc	Gastric resection	Ulcer not removed. Death from hemorrhage on 3rd postoperative day.

The results in patients under 50 years, not subjected to operation, are impressive. Although it is unlikely that the mortality rate for this group could be kept at zero indefinitely we do agree with Allen[15] and Wangensteen[16] that the death rate should be under 5 per cent and probably well below this.

Allen[15] in his study of this problem has come to the conclusion that if surgery is to be undertaken in patients under 50 years of age it is difficult to visualize a mortality rate of less than 5 per cent, if an adequate operation is carried out. He defines as adequate some type of gastric resection which controls the blood supply of the gastroduodenal, right gastric and gastroepiploic arteries.

The problem of surgical intervention in the patient who has survived a severe hemorrhage is a difficult one. Hinton[17] has shown that a high percentage of patients suffer only one severe hemorrhage and Lahey[18] in a study made at his clinic found that of 100 patients treated by a high gastric resection with removal of the duodenal ulcer, 28 bled at some time subsequent to the operation. Five of these patients were proven to have jejunal ulcers.

SUMMARY AND CONCLUSIONS

1. The total mortality in a group of 177 consecutive patients suffering moderate to severe hemorrhage, from duodenal ulcer, was 6.2 per cent.
2. Nonoperative treatment of 165 patients resulted in 7 deaths, a mortality of 4.2 per cent.
3. Operative treatment of 12 patients suffering from severe and uncontrolled hemorrhage was followed by 4 deaths, a mortality of 33.3 per cent.
4. Operation apparently saved the lives of four patients in this series but at the same time it appears probable that some of the patients subjected to operation might have survived without surgical intervention.
5. The occasional indications for surgical treatment of bleeding duodenal ulcer are limited with few exceptions to patients over 50 years of age.

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THE EFFECT OF INJURY ON WOUND HEALING*

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FROM THE PHYSIOLOGICAL DEPARTMENT OF KAROLINSKA INSTITUTET (CHIEF: PROF. U. S. VON EULER) AND THE SURGICAL DEPARTMENT OF KRONPRINSESSAN LOVISAS BARNSJUKHUS (CHIEF: PH. SANDBLOM)

THE NATURE of the initial force in wound healing still remains an unsolved problem. In 1892 Wiesner[23] suggested that injured cells release substances which stimulate normal cells to multiply, and in 1921 Haberlandt[13] proved that damaged *plant cells* release a substance which promotes proliferation of other living cells of the same kind. He called this substance a wound hormone. In 1912 Carrel[3] discovered that embryonic tissue juices stimulate epithelial cells and fibroblasts *in vitro* to intense proliferation.

Fischer[10] found in 1930 that *tissue cultures in vitro* grew faster after being traumatized. He believed that a phospho-protein or a nucleo-protein was responsible for this effect. It has not as yet been possible to decide, however, whether wound healing in living organisms is initiated and promoted in the same manner. The hypothesis lay close at hand that if such substances were produced by wounds in living organisms they could be released into the circulation and promote healing in other parts of the body. Several investigators, among them Lorin-Epstein,[18] 1927, and Fränkel,[12] 1928, reported observations to support this hypothesis, but it was not until 1941 that Young, Fisher and Young[24] gave evidence that was statistically satisfactory.

They made superficial skin defects on the backs of rabbits, measured the healing rate planimetrically, and found that if secondary wounds were inflicted 10–12 days after primary wounds, the former healed more rapidly than the latter. At the same time the present author was studying how the healing of sutured cutaneous incisions was affected by different local and systemic factors. For mensuration of the healing process the tensile strength (T.S.) of the wounds was tested by the method originally described by Chlumsky,[4] 1899, and further developed by Harvey[14] and Howes and Harvey,[15] 1930. The results of this work were reported in 1944.[19] Among the various control series there was one in which symmetrical wounds were made with an interval of 7–13 days between them. It was found that the rate of healing of the secondary wounds as expressed by their T.S. on the 5th to 7th day was greater than that of the primary wounds. This finding supported the results obtained by Young *et al.* and showed that in sutured incised wounds the fibroplasia as expressed by the returning T.S. is accelerated if the organism is already engaged in a healing process.

The following experimental series demonstrates this healing-promoting effect. For technical details and statistical considerations the reader is referred to the author's previous work.[19] In a series including 11 rabbits, two

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incisions, one in front of the other, were made on the back of each. After exactly five days the wounds were excised and their tensile strength (T.S.) measured using a tensiometer (first observation T.S. Gm.). Fifteen days after the first wounds had been made two new incisions were made on the other side of the body, strictly symmetrical with the first ones. These were also excised on the fifth day and measured in the same way (second observation T.S. Gm.). The values obtained representing the T.S. in grams are shown in the table.

TABLE I.—*Wound age 5 days, interval 15 days.*

No.	First Observation T. S. Gm.	Second Observation T. S. Gm.	Relative Difference Second Minus First Observation	Mean
9	196	365	60	54
	260	423	48	
10	358	453	23	30
	246	360	38	
11	266	337	24	11
	258	252	−2	
12	208	357	52	81
	142	492	110	
15	367	634	53	50
	311	510	48	
16	420	810	63	56
	406	668	49	
27	292	355	19	−10
	412	277	−39	
29	240	454	62	79
	206	590	96	
30	345	570	49	28
	308	333	8	
35	495	379	−27	22
	200	416	70	
36	187	203	8	8
	(103)	(450)		

n = 11 m = 37.2 ± 8.84 σ = 29.3 M = 45.7

The relative difference given for each pair is the difference between the second and the first observation in per cent of their average. The mean (m) from the whole series is an expression of the difference between the second and first observation and has been used for examination of statistical signifi-

cance. (A modification of m written $M = \frac{100\,m}{100 - \frac{m}{2}}$ has a more obvious meaning: it expresses in per cent the increase or decrease in T.S. of the second observation in comparison with the first.)

The results are shown in the diagram (Fig. 1), in which the mean of the T.S. of the two primary wounds is represented by a white rectangle. It has

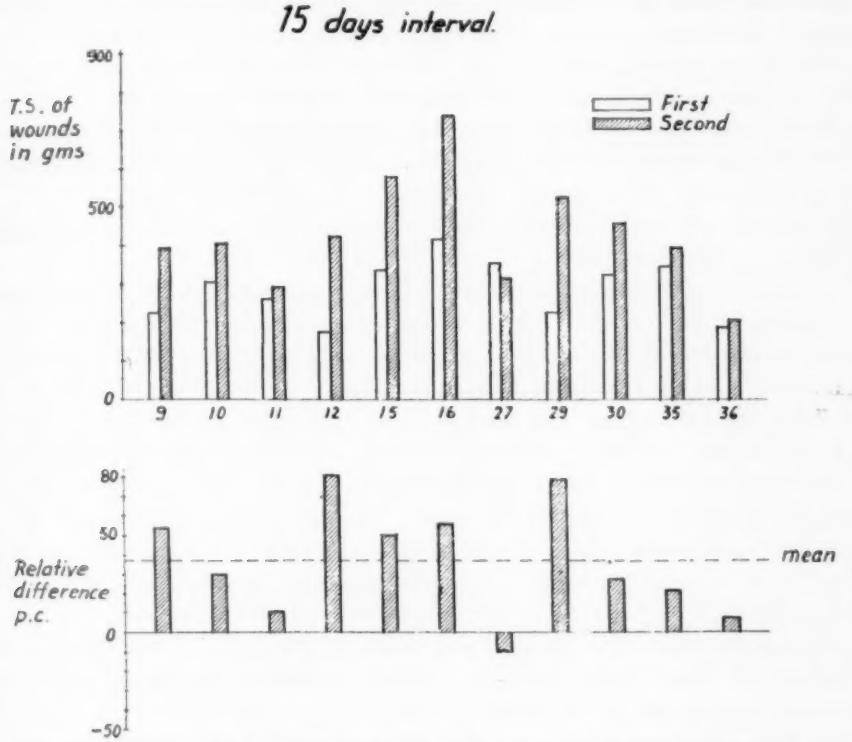

FIG. 1.—The upper diagram shows the T.S. of the primary wounds as white rectangles and the T.S. of the secondary wounds as shaded rectangles. The lower diagram shows the relative difference between the T.S. of the secondary and the primary wounds. The interval between the infliction of the primary and the secondary wound was 15 days and the T.S. was measured on the 5th day throughout.

been put next to a shaded rectangle representing the same values for the secondary wounds. The mean relative difference in per cent has been represented on the lower graph. When it is positive it means that the secondary wounds were stronger than the primary ones; when it is negative they were weaker.

It may be seen from Table I and Figure 1, that the secondary wounds were stronger than the primary wounds in all instances but one, and that the mean difference is $37.2 \pm 8.84\%$ which is a statistically significant value.

The cause of this healing-promoting effect is not known. It is not likely that it is due to local influence, as the wounds were made far apart on opposite

sides of the body—that is to say, in sections with separate circulation. (The secondary wounds might heal under somewhat increased tension after the primary wounds have been excised but the difference, if any, is probably insignificant. Weiss[22] has shown that tension has a directive effect on tissue growth *in vitro*.)

If the cause is a systemic change there are several possible explanations. The oldest is the "wound hormone" concept. As mentioned above, such substances have been shown to be released by injury to plants and to tissue cultures *in vitro*. For more information the reader is referred to an article by Davidson,[9] a monograph by Fischer[11] and articles by Cook and Fardon *et al.*[5] and by Loofbourow and associates.[17] Through the investigations of the latter some knowledge has been obtained concerning the nature and production of growth-promoting substances in tissues *in vitro*. In contrast to this is the fact that in living organisms the existence of such growth-promoting substances is still hypothetical, although the neuro-regenerative growth substance of v. Muralt[16] might be of this type.

Another possible explanation of the healing-promoting effect is that it may be related to the catabolic phase of protein metabolism that follows injury (Cuthbertson[6])—in other words, that it is a phase of the so-called adaptation reaction (Selye[20]) associated with hyperactivity of the adrenal cortex.

This relation may be conceived in many ways, the simplest being that the increase in protein breakdown products in the circulation offers a richer supply of nutrition for the proliferating fibroblasts. Cuthbertson[7] believed that the changes which he had found to occur after injury were the result of the organism's catabolizing its reserves to meet the exigencies of repair. A combination of "wound hormone" mechanism and protein catabolism should also be considered.

It was felt that more data on the action of the healing stimulating effect would be of value in the search for an explanation of its nature and cause. The following questions seemed to be of primary interest:

1. The changes occurring in the healing-promoting effect with the passage of time.
2. The difference between the healing curves of the primary and the secondary wounds.
3. The relationship between the extent of injury and the degree of the healing stimulating effect.

The wide variation in the rate of wound healing in different individuals and also in the same individuals at different times combined with the great experimental errors associated with available methods necessitated a large number of experiments to procure values that would permit estimates and comparisons. Hence in the diagrams shown each point is based on the examination of, in general, at least 40 wounds in at least ten rabbits. The corresponding tables, of which Table I is an example have been omitted and only the resulting m-values with the corresponding standard error have been given in the diagrams.

A major drawback to the method which may be mentioned is that the primary or control wound is identical with and hence inseparable from the stimulus, *i.e.* the injury. When therefore the control is altered—for example, for studying the strength of wounds at different stages in order to construct the healing curve—the stimulus is changed accordingly. Moreover, the injury is two-fold—it consists of inflicting the wound and excising it later for examination. These facts must be borne in mind when the results are evaluated.

For the experiments 800 wounds from 200 rabbits were examined.

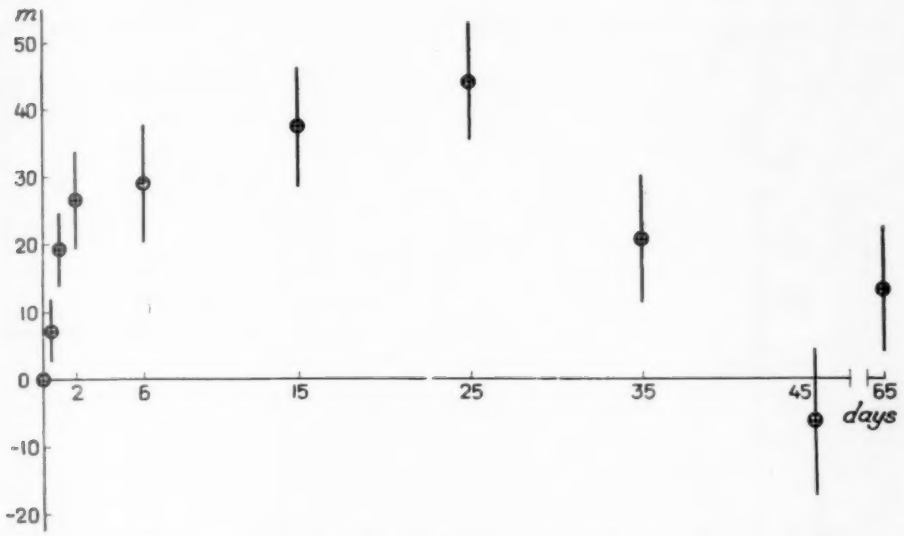

FIG. 2.—The mean relative difference between the T.S. of the secondary and the primary wounds (= the healing-promoting effect) is represented on the vertical axis. The interval in days between the infliction of the secondary and the primary wounds is represented on the horizontal axis. The T.S. was measured on the 5th day throughout.

I. THE CHANGES OCCURRING IN THE HEALING-PROMOTING EFFECT WITH THE PASSAGE OF TIME

Nine groups with at least ten rabbits in each were used. The secondary wounds were made 12 and 24 hours, 2, 6, 15, 25, 35, and 65 days after the primary wounds respectively. The results are shown in the diagram (Fig. 2), each value with its standard error. The curve shows a steep rise the first two days, a flat summit up to the 25th day, and then a slow decrease towards the 45th day. The standard error increases with the time interval. This is supposedly due to the fact that uncontrolled changes in the condition of individuals occur with increasing frequency. As there was a suggestion of a negative phase at the 45th day this group was enlarged to include 16 animals, but the suspicion could not be verified. If some individuals have a negative phase others might still be in the positive phase and the two would thus tend to neutralize one another. As the healing rate was expressed as the T.S. on the 5th day, the graph does not show the actual origin of the healing-promoting

wound effect—only that it is in action before five days and twelve hours after the first part of the injury.

II. THE DIFFERENCE BETWEEN THE HEALING CURVES OF THE PRIMARY AND SECONDARY WOUNDS

Eight groups were used in which the wounds were tested when they were 1, 2, 3, 4, 5, 6, 7, and 10 days of age respectively. Each group included ten rabbits except those for the second and third days, which were made larger (15 and 16 respectively), as it proved to be of interest to compare values from these two days. The interval between the primary and secondary wounds

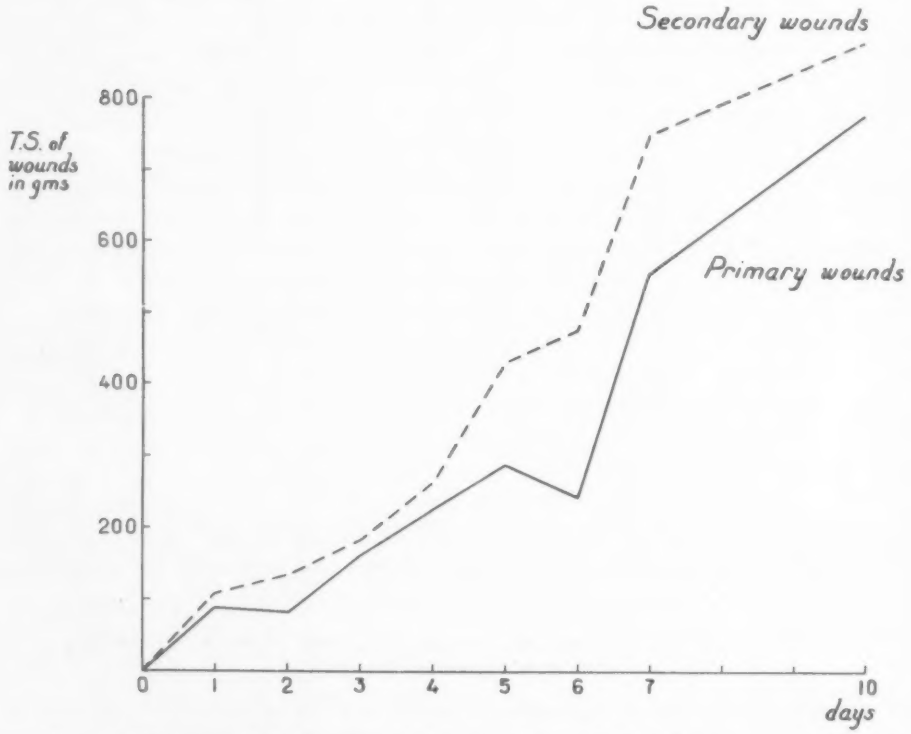

FIG. 3.—The mean T.S. in grams of the secondary and the primary wounds is represented on the vertical axis and the day on which the T.S. of the wound was measured, on the horizontal axis. The interval between the infliction of the primary and the secondary wounds was 15 days throughout.

was made fifteen days because the healing-promoting effect seems to be at its height at this period and rather stable. (Fig. 2.) The healing curves for the primary and secondary wounds obtained from the means of the absolute values are shown in Figure 3 and the means of the relative differences in the T.S. of the primary and the secondary wounds are shown in the diagram Figure 4, in which the standard errors have also been represented.

It will be seen that the secondary wounds were stronger than the primary wounds throughout the whole period examined. As seen from Figure 4, the

difference is statistically significant on the 2, 5, 6, and 7 days. This diagram also shows that the relative difference reaches a maximum on the second day and again on the sixth day. The difference between the m-values from the second and third day is significant. In this series also the injury varied, as the wounds were excised after from one to 10 days. As the interval between the primary and the secondary wounds had been made as long as 15 days, this variation is perhaps not very disturbing, as the previous series showed the

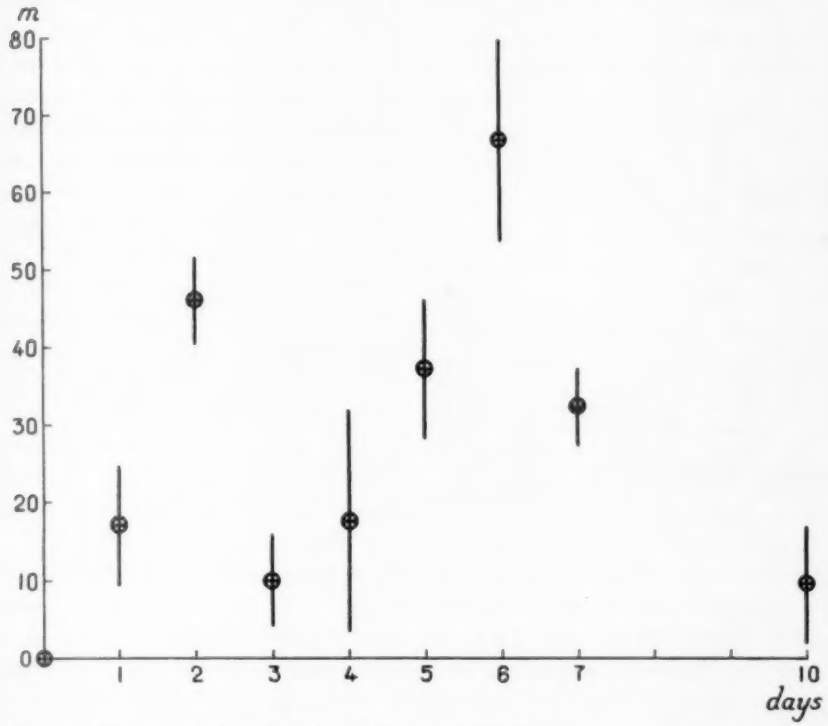

FIG. 4.—The mean of the relative difference in T.S. of the secondary and the primary wounds is represented on the vertical axis and the day on which the T.S. of the wound was measured, on the horizontal axis. The interval between the infliction of the primary and the secondary wounds was 15 days throughout.

healing-promoting effect to be rather stable in the period between 5 and 15 days.

III. THE RELATIONSHIP BETWEEN THE EXTENT OF THE TRAUMA AND THE DEGREE OF THE HEALING-PROMOTING EFFECT

Three series were studied with 12, 11, and 10 rabbits in each respectively. The wound age was 5 days, and the interval between primary and secondary wounds was 15 days.

In the first group only one pair of wounds was made, in the second which has been used in the foregoing series as well, two pairs were made, and in the third group a long cutaneous incision was made in the abdomen when the

primary wounds were excised. The mean differences with their standard error is shown in the fifth diagram (Fig. 5). It will be seen that the healing-promoting effect was greater when the injury was more extensive. The difference is not significant, but may be called highly probable.

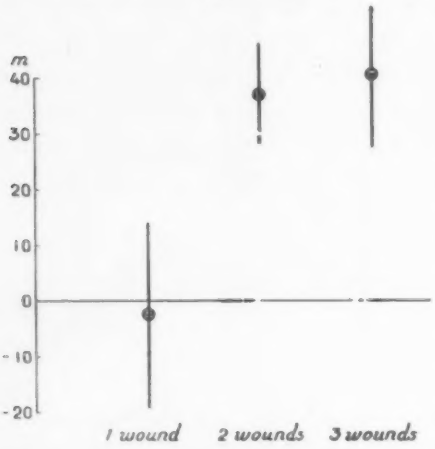

FIG. 5.—The mean relative difference between the secondary and the primary wounds is represented on the vertical axis and the number of wounds inflicted, on the horizontal axis. The interval between the infliction of the primary and the secondary wound was 15 days and the T.S. was measured on the 5th day throughout.

DISCUSSION

Ad. 1. The second diagram (Fig. 2) shows that the healing-promoting effect increases rapidly during the first week after the injury, reaches its full effect 3–4 weeks afterwards, and then gradually disappears towards the sixth week. The healing-promoting effect thus follows the activity of the healing process in the primary wound but continues into the period of cicatrization. It closely follows the curve for the catabolic phase of protein metabolism after injury (Cuthbertson[8]) and thus may well be related to this process. Nothing is known about specific growth promoting substances elaborated from the wound and the results speak neither for nor against this hypothesis.

Ad. 2. The healing rate of the secondary wounds is more rapid than that of the primary wounds from the first day till past the tenth day of healing (Fig. 3). The healing curve of a wound is the effect of at least two processes (Harvey[14]). There is, to start with, a lag period during the first days when the wound edges are kept together only by the wound coagulum. Then comes the period of fibroplasia when proliferating fibroblasts grow across the wound and connect the edges. The fact that the healing curve of the secondary wounds exceeds that of the primary wounds through both of the periods suggests that both of the processes mentioned are influenced by the healing-promoting effect.

When the secondary wound is stronger than the primary one as early as on the first and second day of healing it must be due to a change in the quality of the wound coagulum, as the fibroplasia hardly can have any influence at this early stage. This finding is in agreement with the experience of Bauer,[2] Selye[21] and Cuthbertson.[8] Bauer[2] studied the coagulation of blood in connection with operations. He found the strength of the coagulum markedly elevated 24 hours after operation as compared to before. Selye[21] and his group have had the same experience. Cuthbertson[8] found that the fibrinogen fraction was often appreciably raised during the catabolic phase of protein metabolism.

The increase in the general healing curve beginning after the first day is due to the beginning of fibroplasia (Harvey[14]). When the secondary wounds are stronger than the primary during this period it is to be inferred that the healing-promoting effect stimulates fibroplasia. This could be explained either as an indirect effect through the change in the quality of the wound coagulum or as a direct effect on the fibroplasia. The form of the curve in Figure 4 with two separated maxima for the healing-promoting effect suggests that the fibroplasia is influenced independently of the coagulation. The experiences of Alrich and Lehman[1] that anticoagulant drugs caused a decrease in the healing process as late as on the fourteenth day indicates, however, that even the later part of the healing curve may be influenced by differences in coagulation.

Ad. 3. The probable relationship between the extent of injury and the degree of the healing-promoting effect as illustrated by Figure 5 is in agreement with the findings of Young, Fisher and Young[24] that the difference between the healing rates of the primary and the secondary wounds increases as the surface area of the wound increases. Bauer[2] found that the increase in the strength of the coagulum that occurs in connection with operations was more marked after thyroidectomies than after minor operations such as tonsillectomies (70:40).

SUMMARY

If symmetrical incisions are made successively in the skin of rabbits, the secondary wounds will heal more rapidly than the primary.

Different phases of this healing-promoting effect have been studied. The tensile strength (T.S.) of the wounds has been used as a measure of their healing rate.

1. The healing-promoting effect appeared within five and a half days after injury. It increased rapidly for a few days and reached its maximum between the first and the fourth week after the injury. During this time the secondary wounds were 30–40% stronger than the primary ones on the fifth day of healing. The healing-promoting effect disappeared 6–7 weeks after injury. This course resembles the curve of the post-traumatic catabolic phase of protein metabolism.

2. The healing curve of the secondary wounds exceeded that of the primary wounds through the ten first days of healing. The relative difference between the T.S. of the primary and the secondary wounds had two maxima, one on the second day and one on the sixth day of healing. This suggests that both coagulation and fibroplasia are influenced by the healing-promoting effect.

3. There was probably a relationship between the extent of the injury and the degree of the healing-promoting effect.

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THE SURGICAL MANAGEMENT OF CHRONIC RECURRENT INTESTINAL OBSTRUCTION DUE TO ADHESIONS*

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ONE OF THE MOST DIFFICULT PROBLEMS the internist and surgeon are called upon to manage is the patient who has been subjected to several laparotomies for the lysis of adhesions causing recurrent intestinal obstruction. As a rule after each operation the situation grows progressively worse following a transient period of improvement. Many of these patients become "intestinal cripples" and some become addicted to morphine in order to alleviate the chronic abdominal pain.

Boys[1] in 1942 critically evaluated the many methods recommended for the prophylaxis of peritoneal adhesions. He found all of the methods unsatisfactory with the exception of the intraperitoneal instillation of heparin. He pointed out, however, that although the method was effective in animal experiments, clinical experience was limited to 14 patients, one of whom died postoperatively from a massive intraperitoneal hemorrhage. We are familiar with the data on another patient in whom the outcome was fatal (22 hours postoperatively) due to a massive intraperitoneal hemorrhage.

More recently Bloor and his associates[2] carried out an extensive series of experiments on rabbits in an attempt to evaluate the effect of heparin in controlling the formation of adhesions and reformation of adhesions following lysis. They concluded that heparin was not effective from either viewpoint and further that many of the rabbits succumbed as a result of intraperitoneal hemorrhage and also hemorrhages into vital organs.

In view of the rather hopeless attitude of the profession towards the solution of the problem of recurrent adhesions, it is remarkable that an almost unrecognized and little known method of management has been available since 1937 when Thomas B. Noble, Jr.[3] described his operation of plication of the small intestine. He subsequently reported further continued success with the method in 1939, 1942, 1943 and 1945.[4] Although no statistics are given as to the number of cases operated upon for intestinal obstruction due to adhesions Noble states that "no case plicated has had to be reoperated for obstruction or adhesions."

As a result of the experience obtained with the Noble operation of plication carried out on the three subjects to be reported in this paper we believe that this technic represents a significant advance in surgical therapeusis. The basic principle of this operation is that although reformation of adhesions cannot be

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prevented following their lysis, they can be *controlled*. When this is done successfully, normal motility is restored to the small intestine with consequent freedom from pain, resumption of a proper food intake, and adequate absorption of the necessary nutrients. For the technical details of the procedure the reader is referred to the papers of Noble.[3, 4]

CASE REPORTS

Case 1.—Extreme malnutrition and vitamin deficiency because of adhesions. F. S., a 38-year-old white married woman consulted one of us (N. J.) in December, 1945, complaining of a sore tongue, dependent edema, weakness, vomiting, loss of weight (from a normal of 110 to 95 pounds) and abdominal pain.

The patient was well until 1921 when at the age of 14 years she was operated upon for acute appendicitis. Within one month she was reoperated upon for intestinal obstruction due to an intra-abdominal hernia. During the next year she was operated upon three times for lysis of adhesions, being carried out on each occasion for intestinal obstruction.

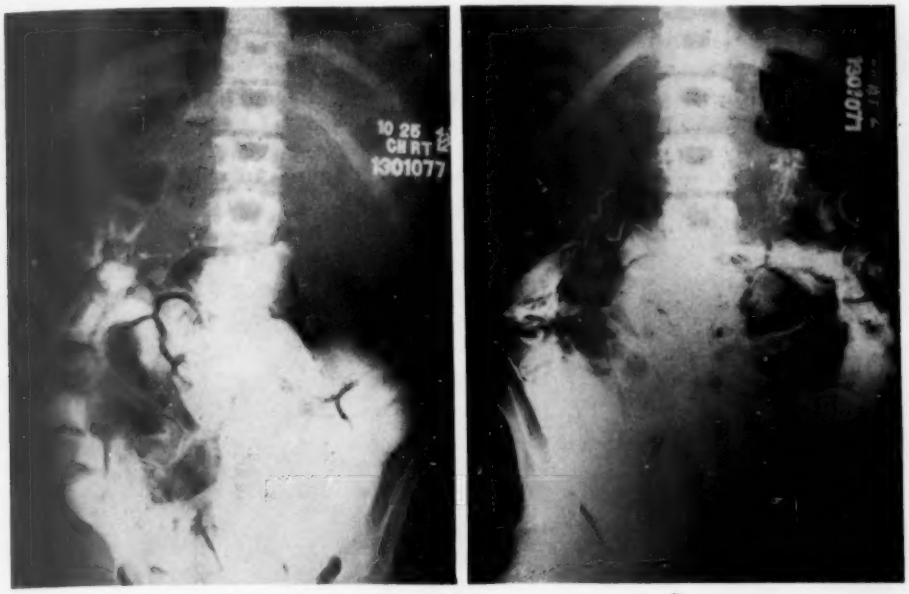
TABLE I.

No.	Date	Operation
1.	June 1921	Appendectomy
2.	July 1921	Exploratory laparotomy—release of an intra-abdominal hernia
3.	August 1921	Ventral hernioplasty—lysis of adhesions
4.	November 1921	Laparotomy—lysis of adhesions
5.	May 1922	Laparotomy—lysis of adhesions
6.	January 1925	Laparotomy—lysis of adhesions
7.	March 1932	Laparotomy—lysis of adhesions
8.	April 1932	Laparotomy—lysis of adhesions and entero-enterostomy
9.	November 1934	Laparotomy—lysis of adhesions
10.	November 1939	Laparotomy—lysis of adhesions and removal of a pelvic cyst
11.	May 1940	Laparotomy—lysis of adhesions and cholecystectomy
12.	June 1942	Laparotomy—lysis of adhesions, and removal of right ovarian cyst and right tube

Two more operative procedures of a similar nature were necessary in 1925 and March, 1932. In April, 1932, in addition to lysis of adhesions an entero-enterostomy was performed. By 1942, 4 more operations were carried out for obstruction and adhesions; in all 11 operations. From 1932 the patient had experienced abdominal cramp-like pain the major portion of each day. By 1938 the patient had become addicted to morphine, necessitating one half of a grain (.03 Gm.) every 2 to 3 hours for control of her pain.

In spite of all these operations the patient's general condition gradually deteriorated (Table I). In October, 1943, the patient was carefully studied in the Mayo Clinic. Gastrointestinal roentgen ray series showed marked delay in emptying of the small intestine (Fig. 1, A and B). The blood calcium was 5.9 mg. per cent, the serum proteins 5.4 Gm. and the plasma ascorbic acid was 0.5 mg. per cent. After one week of intensive nutritional therapy the patient improved and during the next year maintained a fair state of health although the abdominal pain was present daily. In September, 1944, the gastrointestinal roentgen ray series taken at the Mayo Clinic again showed the same delayed emptying time but the blood calcium had risen to 9.8 mg., the serum proteins were 7.3 Gm. and the plasma ascorbic acid was 1.1 mg. per cent. During the next 15 months the patient had many hospital admissions for exacerbations of the intestinal obstruction but these had responded temporarily to gastric suction and parenteral fluids.

At the time of admission here, the patient appeared chronically ill, underweight and debilitated. The abdomen was distended, tympanitic, tender and scarred from 12 previous laparotomies with a ventral hernia, 12 cm. in diameter, covered only by skin and peritoneum



A B

FIG. 1A.—A film taken 4 hours after ingestion of barium by mouth showing dilatation of loops of ileum with delay in emptying.
B.—Six hour film showing marked delay in emptying of small intestine.

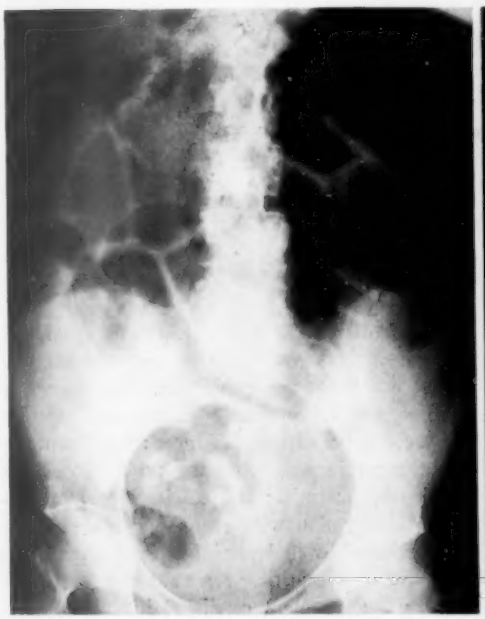


FIG. 2

FIG. 2.—Flat plate of the abdomen showing marked gaseous distention — one week preoperatively.

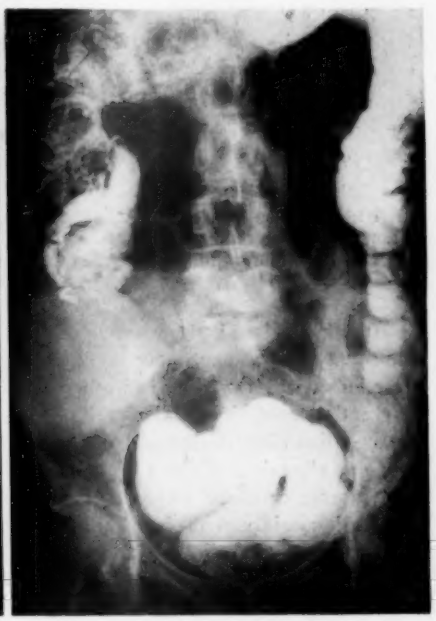
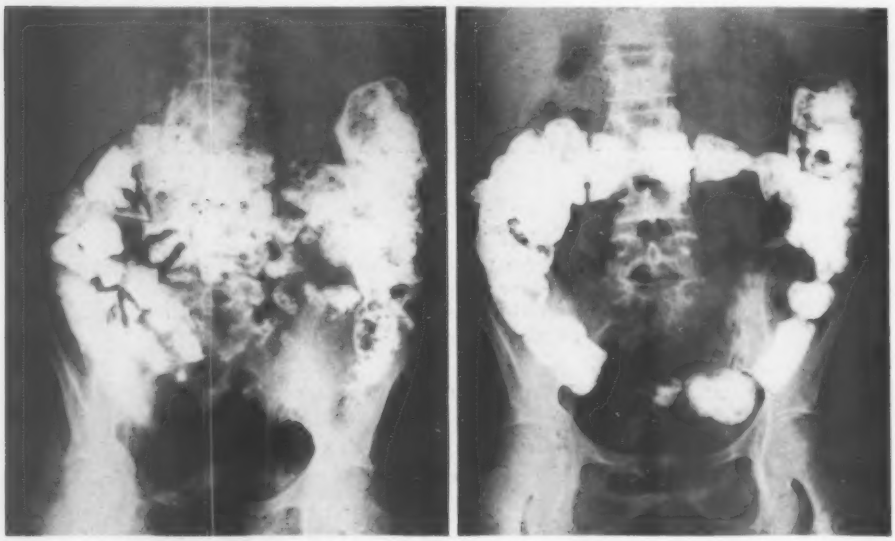


FIG. 3

FIG. 3.—Barium enema demonstrating that the gaseous distention is entirely limited to the small intestine.

through which distended loops of intestine cast their outline. The liver, spleen and kidneys were not palpable; ascites could not be demonstrated; no abnormal masses were felt; digital rectal and bimanual pelvic examinations were negative. Examination for signs of nutritional deficiencies showed the conjunctivae to be thin with only minimal thickening at the equators. Blood vessels of the limbic plexus penetrated a short distance into the true cornea. The angles of the mouth showed both scarring and active fissures. The tongue was thin, completely bald, and showed patches of scarlet-red color at the tip and along the lateral margins. The gums were natural. The skin was slightly dry, tanned, slightly xerotic and showed several ecchymotic areas from accidental trauma. Petechiae could not be produced by the tourniquet test. The extremities showed moderate pitting edema of the feet and ankles. The blood pressure was 120 systolic, 60 diastolic. The heart and lungs disclosed no abnormality. The neurologic examination was normal except for



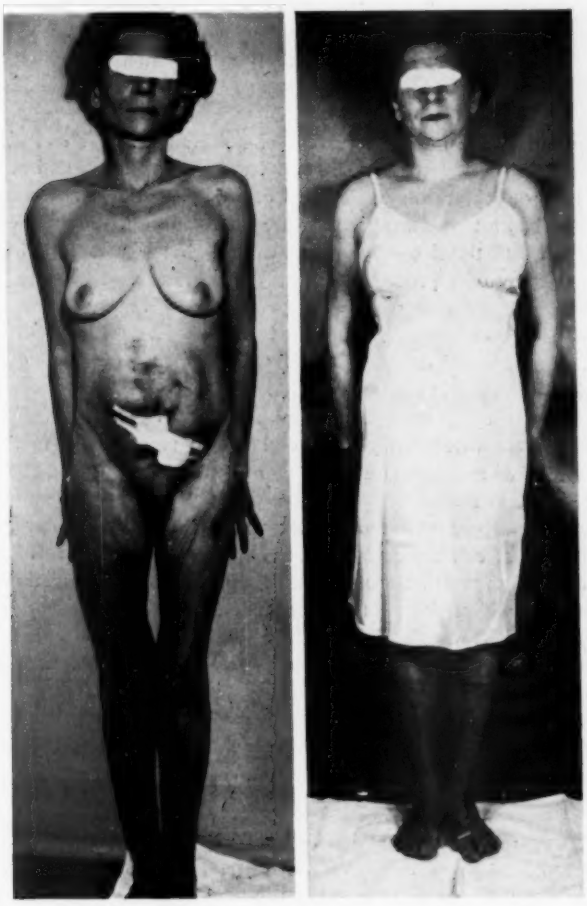
A B

FIG. 4A.—Gastro-intestinal series carried out 2½ months postoperatively. A film taken 4 hours after the ingestion of barium by mouth showing most of the barium in colon. B.—Six hour film showing all of the barium out of the small intestine and in the colon.

dysesthesia of the plantar surface of the feet, and calf muscle tenderness. The red blood cell count was 3,240,000 per cubic mm., the hemoglobin was 10.0 Gm. per 100 cc., the color index was 1.0. The white blood cell count was 9,000 per cubic mm. with a normal differential count. The stained red cells showed no striking qualitative changes. The urine was negative. Blood chemical determinations per 100 cc. of blood showed: total proteins 5.7 Gm., albumin 3.6 Gm.; globulin 2.16 Gm.; ascorbic acid, 0.66 mg.; vitamin A, 28 micrograms; carotene, 133 micrograms; phosphates, 5.4 units; and calcium, 10.0 mg.

A diagnosis was made of chronic intestinal obstruction with secondary malnutrition of calories, protein, minerals and vitamins as manifested by underweight, hypoproteinemia, edema, glossitis, vascularizing keratitis and angular stomatitis. As neither the patient nor her husband would consider surgery, medical management consisted in cajoling the patient into eating as much of a high caloric, high protein, low residue diet as possible, along with supplements of protein hydrolysates and therapeutic amounts of vitamins by mouth. Folic acid therapy orally and parenterally and refined and crude liver extract parenterally failed to produce a reticulocyte response, a rise in hemoglobin or red cells,

changes in the tongue color or texture, or improvement in the angular stomatitis. On two occasions (February, 1946, and June, 1946) the patient was hospitalized for exacerbations of the intestinal obstruction, which responded temporarily to gastric suction and parenteral fluids. On these two occasions intravenous amino acids, blood plasma and whole citrated blood were given, which was followed by a disappearance of the abnormal red color of the tongue but without evidence of papillary regeneration. Within two weeks of discharge from the hospital, however, the redness of the tongue returned.



A B

FIG. 5.—A. F. S., about 2 months postoperatively, weight 78 pounds.
B. F. S., 6 months postoperatively, weight 121 pounds.

On September 8, 1946, the patient was readmitted to Doctors Hospital because of an exacerbation of the chronic intestinal obstruction. Examination was essentially the same as previously described, except that she now weighed but 72 pounds and the pitting edema of the legs and sacrum was more extensive. The chemical examinations were approximately those of December, 1945, except that the vitamin A had fallen to 12 micrograms and the carotene to 16 micrograms, showing failure to absorb the large amounts of vitamin

A she had taken by mouth, and failure to either ingest or absorb carotene in her diet. Hyperperistalsis was evident and dilated loops of small bowel could be palpated readily beneath the skin at the site of the hernia. The rectum was empty. Figure 2 shows a flat plate of the abdomen and Figure 3 a barium enema which demonstrated that all of the dilated loops were of the small intestine.

Following several days of gastric suction, parenteral fluids and blood transfusions, the patient was able to take liquids by mouth. At this time the patient and her husband consented to exploratory laparotomy in hopes of being able to use the Noble plication technic. Sulfasuxidine was administered in 2 Gm. doses every 4 hours for 6 days prior to the operative procedure which was carried out on September 19, 1946, by one of us (J. W. L. Jr.). It consisted in the lysis of the entire small bowel which was completely adherent to itself and to the parietal peritoneum. One area of hopelessly gnarled bowel in the region of the previous entero-enterostomy was resected and it was then necessary to carry out two end-to-end anastomoses to join, first, the distal end of the jejunum to the proximal end of a 3-foot loop which entered the gnarled mass and second, to join the distal end of this loop to the terminal ileum. Continuity having been restored, the remaining 7½ feet of small intestine were then plicated with interrupted sutures of cotton from the ligament of Treitz to the ileo-cecal valve, each limb (or wing) of the plication being 6 to 7 inches long. The entire procedure lasted 5½ hours and necessitated a transfusion of 2500 cc. of blood.

The postoperative course was complicated by jaundice for several days during the first week and the incision and drainage of several subcutaneous abscesses from previously self-administered morphine injections. The patient progressively improved so that by the 30th postoperative day she was without edema and weighed 71 pounds. On discharge from the hospital 3 months postoperatively she weighed 100 pounds. A small bowel roentgen ray series was performed approximately 2½ months after operation and showed a normal emptying time (Fig. 4, A and B).

At the end of one postoperative month demerol was substituted for rapidly diminishing doses of morphine and after another month sterile saline was substituted for the demerol. Two weeks before discharge from the hospital the nature of the injections was explained to the patient and she adjusted well to the complete withdrawal.

During the 16 months which elapsed since discharge from the hospital the patient gained another 20 pounds, has remained free from all signs of intestinal obstruction, and all of the signs of nutritional deficiency cleared (Fig. 5, A and B). Menses which had been absent or scanty for several years returned to normal by the second postoperative month and have remained regular. Normal sized loops of small bowel may be palpated easily beneath the skin at the site of the ventral hernia. There has been no resumption of any narcotic or sedative.

Case 2.—Plication done in presence of acute intestinal obstruction. A 13-year-old colored girl was admitted to Presbyterian Hospital in April, 1947. Appendectomy had been performed without drainage 15 months earlier for acute appendicitis. Ten months later acute intestinal obstruction occurred, necessitating an operation for lysis of adhesions. Six weeks before this admission she was again operated upon for acute intestinal obstruction and a loop of gangrenous ileum was resected; again adhesions were divided. Cramps began 48 hours before this admission associated with continuous vomiting. Examination of the abdomen revealed tenderness and distention. A flat plate of the abdomen showed distended small intestinal loops. The Miller-Abbott tube gave poor relief and operation was carried out because the leucocyte count rose to 22,000 and the temperature to 101.2 in spite of hydration.

At operation (done by E. L. H.) the entire ileum and jejunum were adherent. Many kinks were encountered associated with enlarged mesenteric lymph nodes. There was no evidence of gangrene but dilated vessels were present suggesting early inflammatory change. Interrupted silk sutures were used to plicate entire small intestine. Approximately

6 loops (wings) were made 12 inches in length near the ileocecal valve. All sutures were placed at the mesenteric border so that the entire lumen of the intestine was free. Postoperative convalescence was entirely uneventful. A small bowel series on the 11th postoperative day showed normal motility and emptying of the small intestine. The patient has remained well during the follow up period of 8 months. There has been no dietary restriction and she has had one to two stools a day. Some slight pain and nausea have been noted after menstrual periods.

Case 3.—Case with psychotic manifestation, morphine addiction. A 30-year-old trained nurse had an appendectomy for acute appendicitis 10 years prior to admission to the Presbyterian Hospital in May, 1947. A few months following the appendectomy she was operated upon for intestinal obstruction, gangrenous bowel was resected and adhesions separated and divided. Five years later a cholecystectomy was carried out and adhesions lysed. In 1946 the patient was subjected to 3 operations at 14-day intervals for acute intestinal obstruction due to adhesions. Following the last of these procedures the patient had daily abdominal crampy pain, became addicted to morphine and was classified by the psychiatrist as an "intestinal cripple with conversion hysteria." For 2 months prior to admission the patient experienced constant crampy pain, weight loss and scanty menses.

On the 25th of May lysis of the entire small intestine was carried out followed by plication from the ligament of Treitz to the ileocecal valve by E. L. H. There were many angulations of the small intestine, the wall of which was edematous in spots and there were many enlarged mesenteric lymph nodes. During the first 24 hours postoperatively, the patient experienced severe abdominal cramps which stopped immediately on deflation of the balloon of the Miller-Abbott tube. A small bowel roentgen ray series 6 weeks postoperatively showed normal motility and emptying time. Regulation of constipation proved difficult in this case. During the 7 months follow up the patient has had no abdominal pain, has gained 15 pounds and morphine addiction has been relieved. Rehabilitation was slow, difficult but satisfactory.

COMMENT

Although the period of follow up of 18, 8 and 7 months is brief in the three cases reported above, the remarkable absence of any symptoms or signs of intestinal difficulty following the Noble plication procedure in contrast to the continuous ill health for months and years prior to plication is significant. We believe, therefore, that the results obtained with this operation deserve wider recognition and that the technic will find increasing acceptance among surgeons who are called upon to operate for intestinal obstruction due to adhesions. As Noble has stated, it places the surgeon in control of the formation of adhesions instead of allowing them to form by chance with the possibility of obstructions due to kinking and angulation. Plication of the small intestine is not technically a difficult procedure, and requires only a short time to complete after all of the adherent loops have been freed and adhesions divided, but the separation of the adhesions is a long painstaking procedure. Normal function of the small intestine is promptly restored by the operation and the ingestion and absorption of proper nutrients follow, causing the patients to gain weight and lose manifestations of their deficiencies. Two of the three patients became free of morphine addiction, one of eight years and the other of one year, and following the plication procedure both have been free from its use for 18 and seven months respectively.

CONCLUSIONS

1. The plication operation of Noble changes *uncontrolled* adhesions into *controlled* adhesions thereby preventing further attacks of intestinal obstruction due to this cause. A proper nutritional balance is restored, deficiencies clear and pain disappears. The psychotic and addiction states are relieved.

2. The histories of three cases are reviewed in detail to illustrate the great value of the procedure of plication of the small intestine.

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WEDGE OSTEOTOMY FOR FRESH INTRACAPSULAR FRACTURES OF THE NECK OF THE FEMUR*

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THAT THE PROBLEMS ASSOCIATED with intracapsular fractures of the neck of the femur are not, as yet, totally solved, is becoming more and more apparent as the end result studies from various clinics are being recorded in the literature. Many men are under the erroneous belief that by restoration of anatomic alignment and internal fixation of the fragments they will obtain good end results in 90 per cent or better of their femoral neck fractures. H. B. Boyd and I. L. George reported the following end results in a series of cases from the Campbell clinic:—43.6 per cent good results, 28.1 per cent poor results and 19 per cent fair results. Of the 28.1 per cent poor results, 13.5 per cent were due to nonunion. An end result study of 102 cases of intracapsular fractures of the neck of the femur treated by the author revealed nonunion in 16 cases or 15.6 per cent. These cases were all treated by the orthodox method of reduction and internal fixation. The interesting feature of all these cases of nonunion was varying degrees of absorption of the distal fragment. Regardless of the status of the proximal fragment, whether it was viable or not, the feature of absorption in the distal fragment was always present.

It is generally believed that there are many factors responsible for nonunion such as inadequate reduction of the fragments, severe initial trauma, severed blood supply to the proximal fragment, death of the head and lack of impaction of the fragments. Nevertheless, it is true that many intracapsular fractures do unite in spite of poor anatomic alignment in the presence of a dead head and lack of impaction. It is becoming more and more obvious that there is only one real reason for nonunion and that is inadequate immobilization. If the fragments are adequately immobilized and protected for a sufficient length of time, union should occur in 100 per cent of the cases.

It is general knowledge that the abduction type of femoral neck fracture invariably goes on to bony union. Watson-Jones believes that if these fractures are adequately immobilized union will occur in 100 per cent of the cases. This is not true of the adduction type of fractures which is the most common transcervical femoral fracture. Roentgenologic study of those cases in which the femoral neck was absorbed revealed certain features which are known to all orthopedic surgeons but whose true significance I am sure has been misinterpreted or underestimated. The radiographic appearance of a segment of bone whose blood supply has been totally or partially interrupted reveals no changes in the general architecture of the bone. There is no decalcification, therefore, its density is not changed and in fact, its density may appear to be increased in

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contrast to the adjacent bone with a normal blood supply. The early phases of absorption of a femoral neck fragment reveals generalized decalcification followed later by fragmentation and absorption of the bone elements. This is indicative that destruction of the fragment is not the result of a disturbed blood supply, but due to an over active hyperemic process which causes decalcification, fragmentation and absorption of the bone fragment.

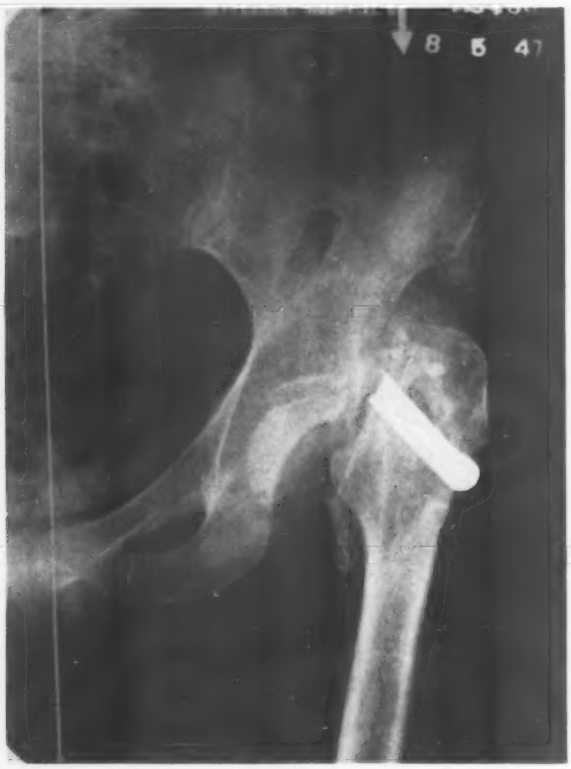


FIG. 1.—Note the complete absorption of the femoral neck following internal fixation with a Smith-Petersen nail. There is no radiographic evidence of a complete or partial loss of blood supply to the neck which would be demonstrated by a normal bone pattern and increased density. The bone trabeculae have disappeared; there is evidence of demineralization of the remaining bone of the base of the neck and of the upper end of the femoral shaft. These findings are consistent with a very active inflammatory process which has caused demineralization, fragmentation, and absorption of the femoral neck.

In the adduction type of fracture there is a shearing force at the fracture line at all times due to contraction of the ilio-femoral muscles. If there is any weight bearing this shearing force is increased; in the presence of inadequate immobilization a traumatic reaction is set up at the fracture site. Hence, conditions are established which are responsible for absorption of the femoral neck.

There are several causative factors which are responsible for inadequate immobilization, the most common being failure to restore and maintain true anatomic alignment. In many instances the fixation pin may be poorly placed, hence, it fails to prevent torsion and shearing strains at the fracture site. Absorption around the fixation pin and at the fracture site is a common feature

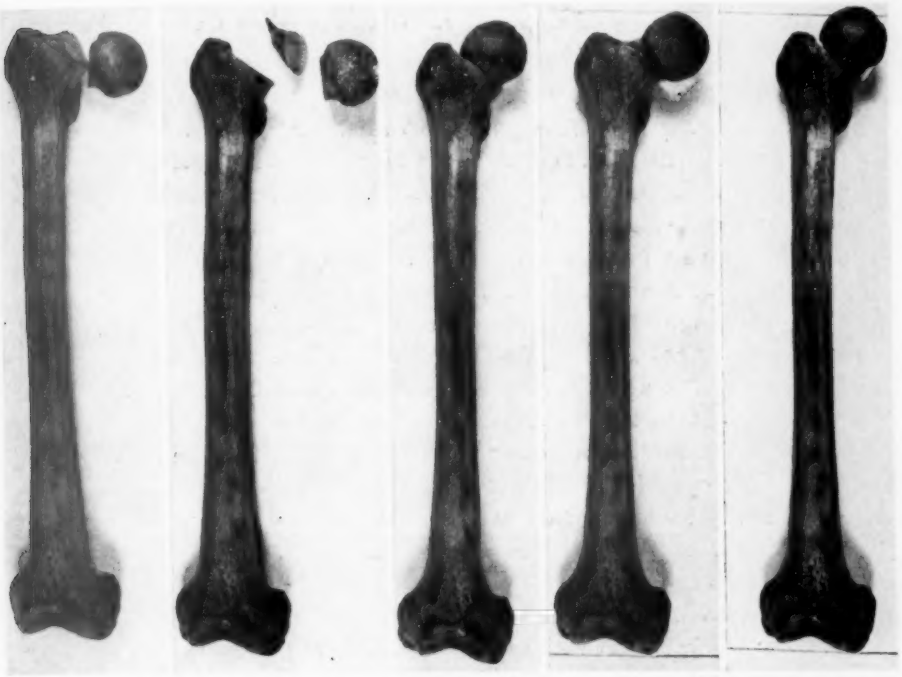


FIG. 2 FIG. 3 FIG. 4 FIG. 5 FIG. 6

FIG. 2.—This figure portrays the usual type of adduction fracture and the relative position of the fragments upon opening the joint capsule.

FIG. 3.—The wedge of bone has been removed from the femoral neck, note its size and shape, and the direction of the osteotomy line through the femoral neck.

FIG. 4.—The femoral head has been placed on the femoral neck in a position of valgus on a wide base. The fragments are fixed in this position by a Smith-Petersen nail.

FIG. 5.—Normal femur—note the position of superior margin of the articular surface of the head to the black line.

FIG. 6.—Same femur as in Figure 5 with a wedge removed from the neck and the femoral head placed in a position of valgus. Note that the superior articular surface of the head now lies above the black line. The length of the femur is actually lengthened by increasing the angle of the femoral neck.

which is followed by loss of adequate immobilization and allows the shearing forces to act freely at the fracture site.

Since we have failed to obtain and maintain continuous adequate immobilization of the fragments in all cases until bony union has occurred (by restoration of anatomic alignment and internal fixation), it becomes obvious that a new and different approach to the problem must be found. This thought prompted the development of a new surgical procedure namely a wedge osteot-

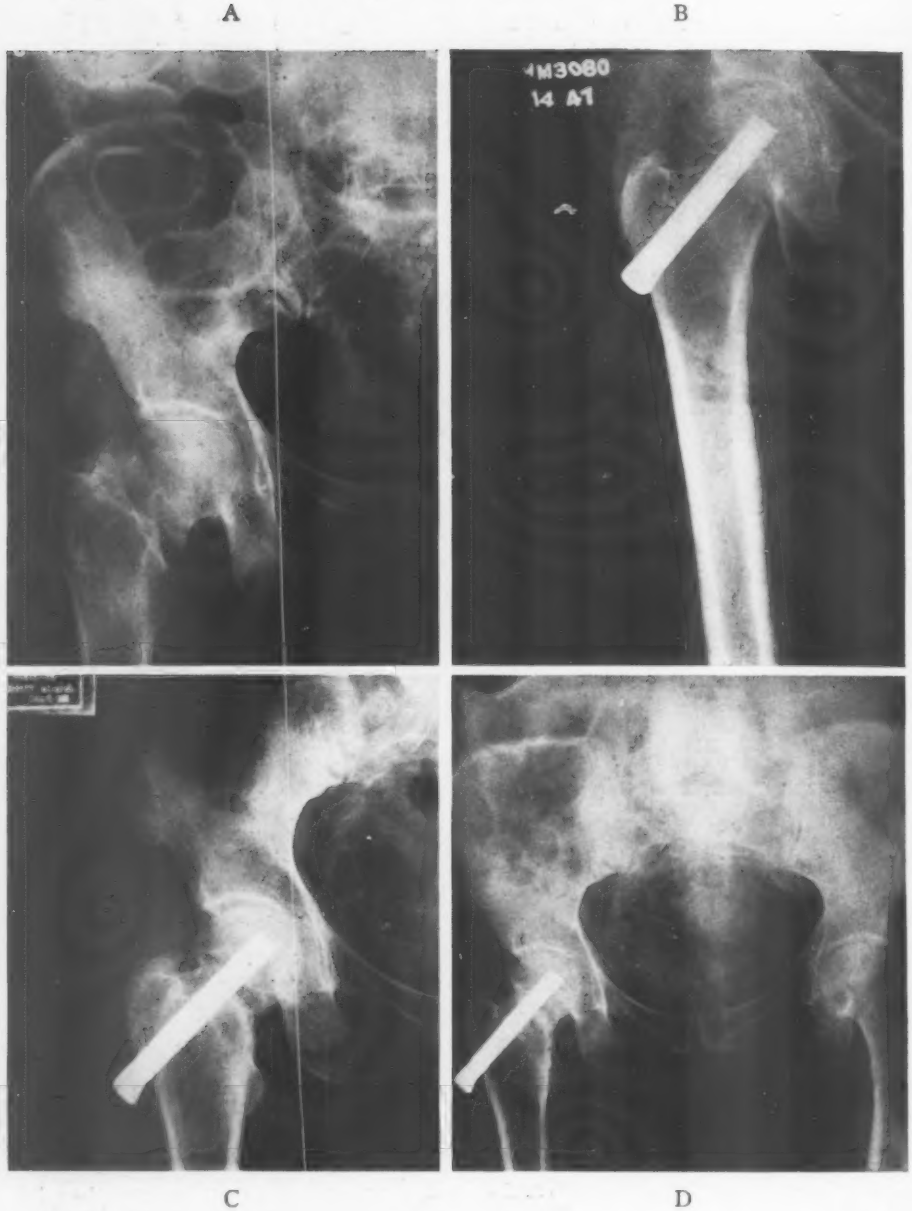


FIG. 7 (A).—Shows an adduction type of fracture with a "beak" shaped projection extending along the inferior aspect of the proximal fragment. This "beak" must be removed to obtain good apposition of the fragments. (B). Is the immediate postoperative roentgen ray film. (C). Note position of fragments and state of bony healing three months postoperatively. (D). Note solid bony union eight months postoperatively. Head shows no evidence of aspectic necrosis.

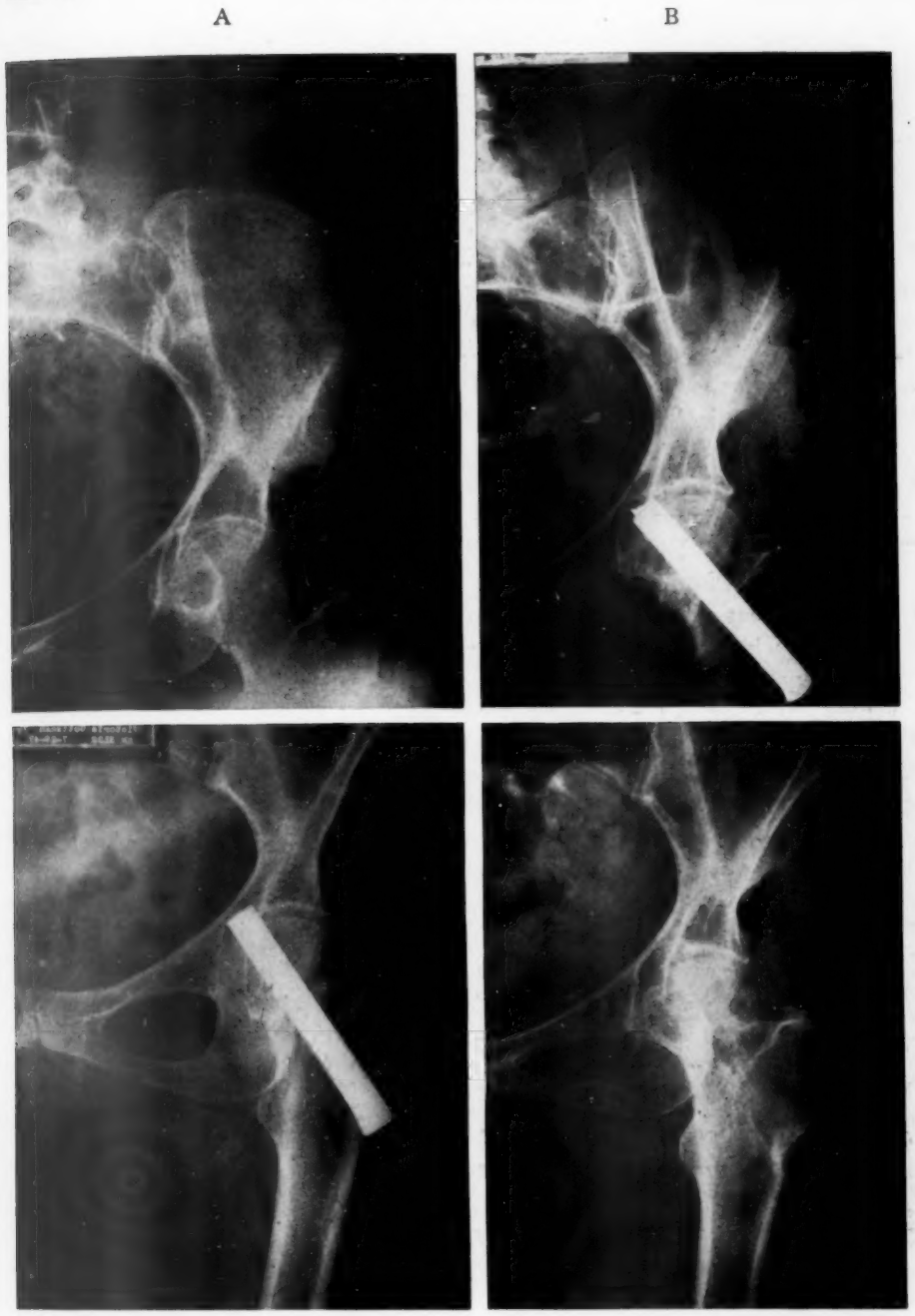


FIG. 8.—(A). Shows an intracapsular fracture in which the fracture line is in a vertical plane. (B). Note position of fragments after a wedge osteotomy was performed. (C). Note evidence of bony healing six weeks postoperatively. (D). Complete healing is evident eight months postoperatively, because the nail had pierced the head on insertion it was removed.

omy through the femoral neck done in fresh adduction fractures. Essentially it consists in the conversion of an adduction fracture to an abduction fracture by removing a wedge of bone from the femoral neck. All shearing forces at the fracture site, regardless of their origin, are now converted into impacting forces which enhance healing. This preliminary report of 22 cases is being submitted with the hope that the procedure will be adopted by more surgeons interested in femoral neck fractures. At a later date the end result studies of a larger series of cases will be presented.

TECHNIC OF OPERATION

The hip joint is exposed through a Smith-Petersen incision which is extended backward to the posterior portion of the tensor fascia femoris muscle. The tensor fascia femoris muscle is divided transversely about 3½ inches to 4 inches below the tip of the greater trochanter. The fracture site is exposed by a vertical incision in the joint capsule. If more exposure is needed, it may be necessary to make transverse incisions in the capsule above and below the vertical incision. By external rotation of the extremity the fracture site is readily brought into view. At this point a very common and important finding should be mentioned. In eight of the cases operated upon to date the proximal fragment, whether it was short or long, possessed an extension of the femoral neck along its inferior aspect. This projection was "beak" shaped and prevented reposition of the proximal fragment into a valgus position; therefore, it had to be removed in every instance. It is obvious that this "beak" would offer great resistance to any closed maneuver which attempted to place the proximal fragment in a position of valgus. This proved to be true at operation; it was impossible to attain the valgus position and still have good approximation of the fractured surfaces unless the "beak" was removed.

The next step is the removal of a wedge of bone from the distal fragment of the neck with its base superiorly and its apex inferiorly. The width of the base depends upon the obliquity of the fracture line. The more the fracture line approaches the vertical the greater the width of the base. The wedge should be of sufficient size so that an adequate support is created for the proximal fragment. The "beak," if present, is then removed with an osteotone from the proximal fragment.

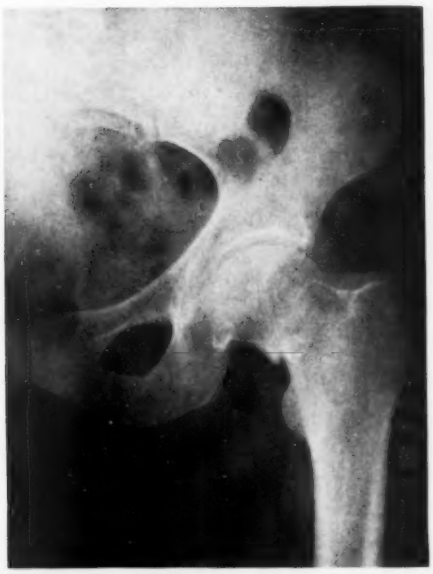
The shaft is next internally rotated and the proximal fragment levered into its new position of valgus. The fragments are locked by internal rotation and abduction of the femoral shaft.

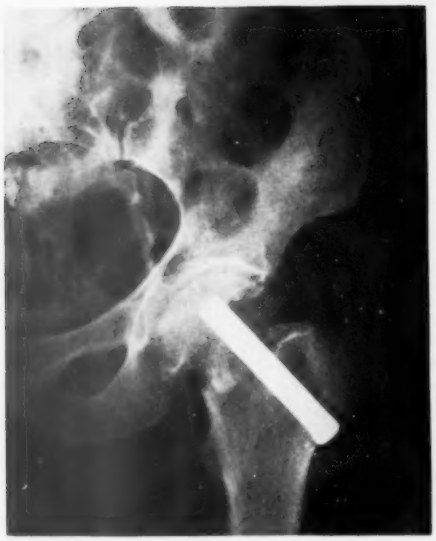
Under direct vision the fragments are locked together with a Smith-Petersen nail. The capsule is closed with interrupted sutures and the incision is closed in the usual fashion.

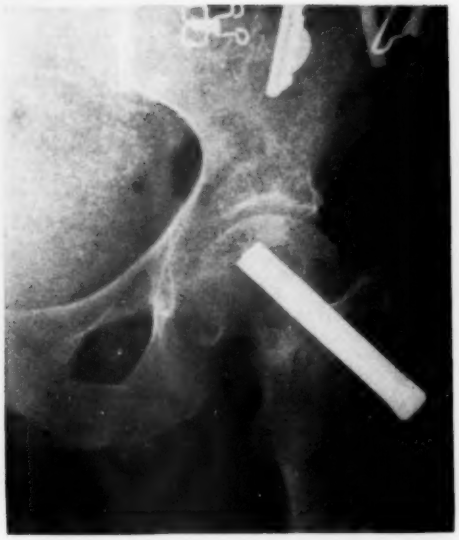
POSTOPERATIVE MANAGEMENT

These patients are allowed to sit at the edge of the bed on the first or second postoperative day. On the third day they are allowed out of bed in a chair and on the fourth day they are made to stand on crutches; partial weight

A



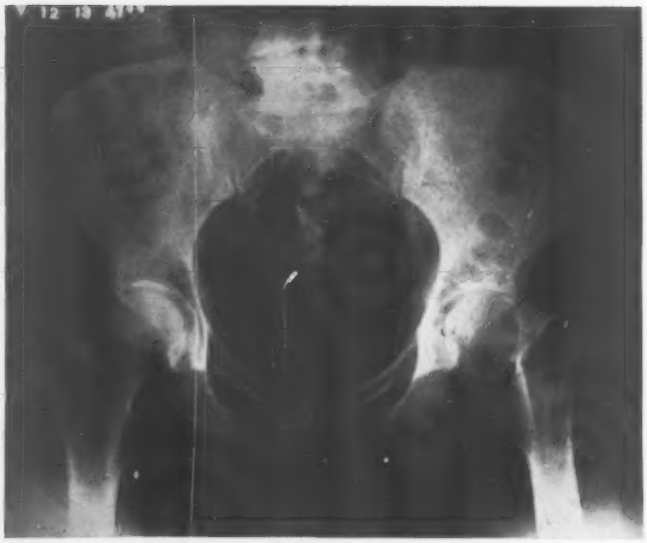


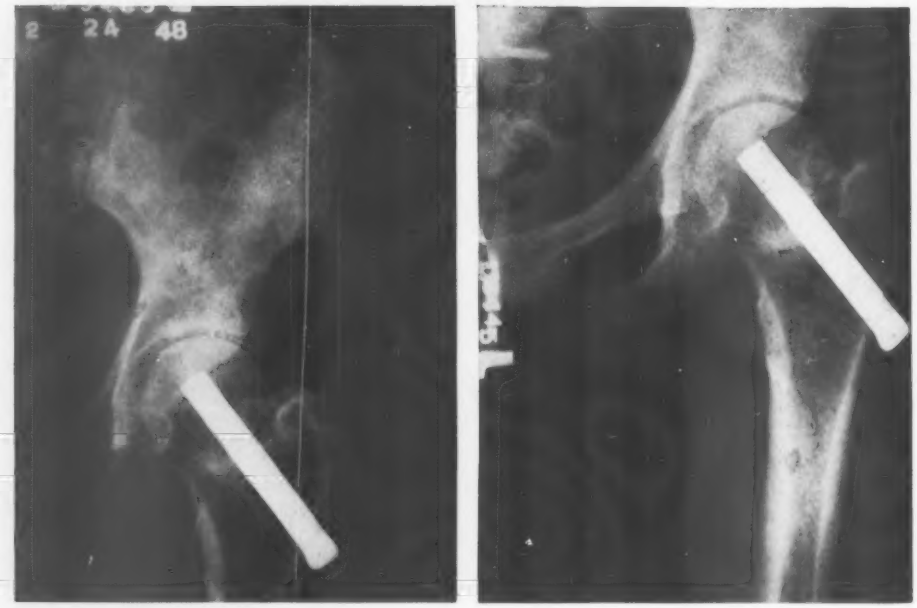


B C

FIG. 9.—(A). Shows typical adduction type of fracture with a "beak" along the inferior aspect of the proximal fragment. (B). Immediate postoperative film. (C). Note status of bony union four months postoperatively.

A





B C

FIG. 10.—(A). Adduction type of fracture with considerable upward displacement of the shaft. (B). Note valgus position of head in immediate postoperative film. (C). Note status of bony union four months postoperatively.

bearing is allowed on the fractured extremity. The patients are ambulatory, on crutches, by the end of ten days. A check-up radiographic examination is made every six weeks and at the end of four and one-half to five months they are made to discard their crutches.

To date no evidence of avascular necrosis of the head has appeared in any of the cases; this, however, may occur at a later date.

ANALYSIS OF CASES

Twenty-two cases with an adduction type of transcervical fracture of the neck of the femur are presented. The youngest patient was 62 years old, the oldest patient was 83 years old. In eight cases the proximal fragment had a "beak" like projection along its inferior surface. A wedge osteotomy was done in each case as described above and the proximal fragment was placed in a position of valgus. The fragments were fixed by a Smith-Petersen nail. Union was obtained in all cases and definite bony union was evident in the check-up radiographic examination 12 to 16 weeks after operation. No absorption of the femoral neck occurred in any of the cases. There was no evidence of loss of position of the proximal fragment or of absorption around the fixation pins. To date no evidence of an aseptic necrosis of the femoral heads has been noted although sufficient time has not yet elapsed to pass final judgment. The first case in this series is 12 months old, the last case is 4½ months old. There were no deaths.

DISCUSSION

In view of the results to date, this is a justifiable procedure. In the hands of men competent in hip surgery this is not a formidable operation. Many orthopedic surgeons today have gone back to the open method of internal fixation of femoral neck fractures; their morbidity and end results do not differ from the end results of those using the closed methods. This procedure adds one more step to the open procedure, namely: the removal of a wedge of bone from the distal fragment. The only real difficulty in the procedure may be the presence of the "beak" of bone on the proximal fragment; this difficulty is overcome by removal of the projecting spicule of bone.

The length of the limb is not sacrificed as a result of this procedure. In fact, the length of the extremity is in most instances increased as much as one eighth to one fourth of an inch. This is due to the extreme valgus position of the proximal fragment. Figures 5 and 6 illustrate this point.

What the fate of the femoral heads is going to be is still undecided. Undoubtedly a certain number will develop aseptic necrosis because of an interrupted blood supply at the time of the initial trauma. In this small series the features of aseptic necrosis as yet have not manifested themselves.

Recent Follow-up Study on Reported Cases

Since this article was submitted for publication, another follow-up study has been made of the reported cases. The oldest case is now 20 months and the

most recent is one year following operation. The survey revealed that all the reported cases united by bony union; however, we have had two instances of asceptic necrosis of the femoral head.

Sixteen other cases have been operated upon. In this second group there were found three cases of absorption of the femoral neck. Two of these cases can be attributed to the fact that the patients insisted upon walking. In the third case failure was due to faulty operative technic. At the time of the operation, considerable difficulty was encountered in aligning the femoral head in a position of abduction. More extensive surgery than is usually required was necessary in order to get proper alignment. One is forced to believe, therefore, that this added trauma and the manipulation was directly responsible for the absorption of the femoral neck.

It might be interesting to note that in two other instances the three-flanged nail would not penetrate the femoral head. In both cases it was necessary to remove the femoral head and do a primary arthroplasty of the hip. After operation the heads were placed upon a wooden block and an attempt was made to drive the nail through. In one instance, the end of the three-flanged nail splintered but did not penetrate the head. In the other instance, the head disintegrated into several fragments but did not allow penetration of the nail. These two cases are recorded because they provide another explanation of why some blind nailings fail. It may be possible that in a small percentage of cases the increased density of the head prohibits any type of internal fixation. A more detailed report will be made on the entire series at a later date.

TISSUE-CULTURE EVALUATION OF THE VIABILITY OF BLOOD VESSELS STORED BY REFRIGERATION*

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For several decades experimental surgeons have been studying methods for the storage of vascular segments and have been working toward the goal of using such stored vessels as grafts whenever it is necessary to bridge a large gap in the arterial or venous system. Vascular segments have been stored in vaseline, moist air, saline, Ringer's solution, and other media, at temperatures slightly above freezing.[6, 7, 8] Vessels have also been stored in a frozen state.[2, 3, 16] To evaluate the viability of a stored vessel, examinations have generally been made by studying its histological detail or by implanting a portion of it as a graft and observing it during a survival period in a living animal. The viability of stored tissues destined for grafts has been tested by tissue-culture methods on only a few occasions,[8, 23] but such tests have not been applied to the study of blood vessels. It is the purpose of the present communication to record our observations on tissue-culture studies which were made on arterial segments (animal and human) which were stored by various methods.**

METHODS EMPLOYED FOR VESSEL STORAGE

First Method—Storage in 10 Per Cent Homologous Serum and Balanced Salt Solution

Portions of aorta or its large branches were obtained under aseptic conditions within five hours after death from mongrel dogs of various ages, young adult human beings, a young baboon, and a young pig. Following ligation of branches with 0000 silk the vessels were divided into segments 2 to 6 cm. long which were suitable for grafting and into control segments 0.3 to 1 cm. long. The vessel sections were held temporarily in sterile "Ringer's"† or balanced

* Submitted for publication, September, 1948.

** This study has been greatly facilitated by the generous assistance of Dr. John F. Enders, The Children's Hospital, Boston, Mass., and Dr. John H. Hanks, Department of Bacteriology, Harvard Medical School, Boston, Mass., who suggested the methods of storage and of tissue culture and guided the project at many stages.

† The "Ringer's" solution had the following composition per liter: NaCl 7 Gm., Na Lactate 2.7 Gm., KCl 0.4 Gm., $CaCl_2$ 0.2 Gm.

salt solution (hereafter called "BSS"),* and as soon as possible thereafter (generally within 30 minutes and always within 2 hours) were placed individually in sterile 25 or 50 cc. Erhlenmeyer flasks containing 10 or 20 cc. of the following nutrient medium: BSS 85 per cent, homologous serum** 10 per cent, penicillin and streptomycin (1000 units each per cc.) 5 per cent. During most of this study, flasks were stoppered with cotton and the volume of fluid was so chosen that it just covered the tissue (Fig. 1.). Segments for tissue-culture or histological control were generally included in the flasks, with the graft segments but occasionally in the earlier part of the work they were placed in separate flasks. Recently it has seemed better practice to close the flasks with a tightly-fitting skirt type rubber stopper. Most of the flasks were stored at 1° to 4° C. in the hospital blood bank refrigerator; a smaller number were held in a common domestic refrigerator, the temperature of which varied between 6° and 11° C. In some instances the nutrient medium was renewed at intervals, generally every two weeks. During storage the flasks were carefully observed for cloudiness, growth of fungi, or changes in pH. In a few instances bacteriological studies were made. These included culture of the centrifuged and washed sediment from the storage media and measurement of

FIG. 1.—Blood vessel stored in flask containing 10% homologous serum and balanced salt solution.

* BSS solution was supplied by Dr. J. H. Hanks. It resembles "Tyrode's" solution and was prepared as follows:

Stock solution, contents per 250 cc.: NaCl 20 Gm., KCl 1 Gm., $MgSO_4$.$7H_2O$ 0.2 Gm., $MgCl_2$.$6H_2O$ 0.2 Gm., $CaCl_2$ 0.35 Gm. (dissolved separately), Na_2HPO_4 0.15 Gm. (0.38 Gm. of Na_2HPO_4 .$12H_2O$), $KHPO_4$ 0.15 Gm., glucose 2.5 Gm., 0.4% phenol red 12.5 cc.

Buffer: 1.4% $NaHCO_3$.

The stock solution was stored at room temperature with 1 cc. chloroform. The final solution was made by diluting the stock 1:10, autoclaving, and adding 0.5 cc. (previously autoclaved) buffer per 20 cc. This was stored in cotton-stoppered containers in the ice-box, which caused pH equilibration at about pH 7.6.

A somewhat similar solution prepared according to Simms' formula is available commercially from Microbiological Associates, Flemington, New Jersey.

** Baboon and pig vessels were stored in dog serum. Fresh or frozen serum was employed.

the antibacterial titer of the storage fluid from time to time.*

Second Method—Storage in Helium under Pressure

Segments of dog vessels were washed in BSS, placed in test tubes, and then stoppered tightly. The air was replaced with medicinal-grade helium at 76 cm. Hg. above atmospheric pressure and the tubes were stored at 0° C.

Third Method—Storage in Salt Solutions

Several experiments were carried out, placing sections of dog arteries in cotton-stoppered 50 cc. flasks in normal saline, "Ringer's" solution, or BSS. In each instance penicillin and streptomycin solution was added (giving a final concentration of each drug of 50 units per cc.). These were stored at 6° to 11° C.

Fourth Method—Storage in 100 Per Cent Serum

Dog vessel segments were placed in 10 cc. of autologous serum in 25 cc. cotton-stoppered flasks. Their refrigeration temperature was 1° to 4° C. No antibiotics were added.

Fifth Method—Storage in Serum Ultrafiltrate, With and Without 10 Per Cent Homologous Serum

Dog vessel segments were placed in 50 cc. flasks containing 20 cc. of fluid which was composed of serum ultrafiltrates** 33 per cent and BSS 67 per cent. To each flask was added penicillin-streptomycin (final concentration 50 units per cc.), and to about half, 2 cc. homologous serum. Approximately half of the tubes were closed with sterile cotton and the remainder with skirt type rubber stoppers. Some of the flasks were stored at 1° to 4° C. and some at 6° to 11° C.

Sixth Method—Storage of Vessels in Frozen State

Segments of dog vessels of varying size were placed individually in sealed 15 mm. Pyrex test tubes or sealed one-half inch heavy copper tubes and frozen in a variety of ways to approximately —70° C. They were all then stored at about —76° C. in a solid carbon dioxide deep-freeze.† When specimens were to be used for grafting or for tissue-culture studies, they were thawed by immersing the tubes for 3 to 10 minutes in a 37° C. water bath.

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* The bacteriologic examinations were kindly performed by George E. Foley, Department of Pathology of The Children's Hospital.

** Serum ultrafiltrate is obtainable commercially from Microbiological Associates, Flemington, New Jersey.

† Most of these experiments were carried out in conjunction with Dr. C. A. Hufnagel, Department of Surgery, Peter Bent Brigham Hospital, Boston, who shared the vessels stored for grafting.

The methods of freezing were as follows:

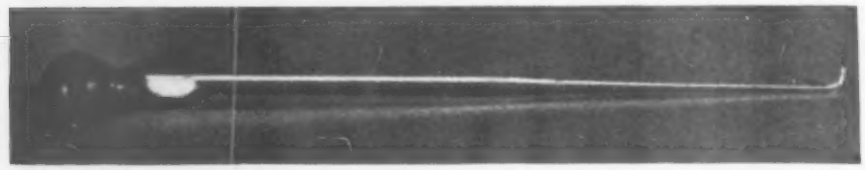
A. Glass tubes containing air at atmospheric pressure were immersed in a mixture of alcohol and solid carbon dioxide.[4]

B. Sealed glass tubes were filled with helium at 20 to 152 cm. Hg. above atmospheric pressure and frozen by immersion in an alcohol-carbon dioxide mixture.[16]

C. Glass tubes with helium at 76 cm. Hg. above atmospheric pressure were slowly brought to —70° C. in about 30 minutes rather than rapidly as in A and B.

D. Copper tubes flushed with sterile mineral oil and filled with helium at about 152 cm. Hg. above atmospheric pressure were immersed in an

FIG. 2



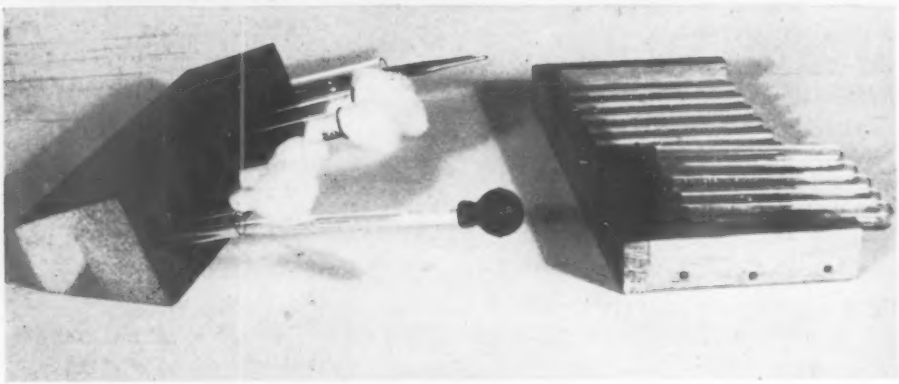


FIG. 3

FIG. 2.—Right angle pipette for transferring tissue to culture tube. Made by drawing out 8 mm. soft, glass tubing.

FIG. 3.—*Left*—Wood block used for holding reagents and Bard-Parker knives. *Right*—Test tube holder employed for setting up cultures and for slanting them in the incubator (after Hanks).

ether-carbon dioxide mixture for very rapid freezing. To ascertain if the copper *per se* was toxic to the tissue, several tubes were not frozen but were stored at 6° to 11° C. instead.

METHODS EMPLOYED FOR TISSUE-CULTURE STUDIES

When a portion of vessel was to be cultured, it was placed in a sterile Petri dish, washed with BSS, and cut into 1 to 2 mm. squares the full thickness of the vessel wall with two No. 11 Bard-Parker knives which had been steril-

ized by storage in 95 per cent ethyl alcohol and ignition of the alcohol. The BSS was then pipetted off and the following transfer medium substituted: Homologous serum* 2 cc., BSS 2.5 cc., beef embryo juice** 0.5 cc., penicillin and streptomycin solution (1000 units each per cc.) 0.5 cc. Sterile acid-cleaned 125 x 15 mm. test tubes were prepared by rinsing their entire lower half with one drop of chicken plasma.† Four pieces of a given tissue were then transferred to each of two tubes with a small right angle pipette (Fig. 2.). After aligning these fragments in the lower one-half of the tube, 4 to 6 drops of the transfer medium were added and the tubes rotated and tilted to mix the medium and the chicken plasma thoroughly (Fig. 4). The tubes were then placed flat, with the tissue down. When firm clotting had occurred (usually after 5 to 10 minutes) 10 to 15 additional drops of medium were added with care to wet the entire surface of the clot. The tubes were then closed tightly with rubber stoppers, slightly slanted (Fig. 3), and place in a 37° C. incubator. Readings were taken at intervals for one, and occasionally two weeks, by examining the edges of the tissue explants for cell growth under low power and by observing changes in pH. Any increase in acidity due to tissue metabolism was shown by change of color from pink (pH 7.4–7.6) to orange (pH 7.2–6.8) to yellow (below pH 6.8). The fluid in the tubes was not renewed but one drop of bicarbonate buffer was added if the fluid became yellow. When growth occurred, a rough index of its extent was obtained by recording the proportion of explant circumference supporting cells. Growth consisted of fibroblastic proliferation. Since endothelium is difficult or impossible to differentiate from this[21] and may actually transform into fibroblasts[27] no special effort was made to distinguish it.

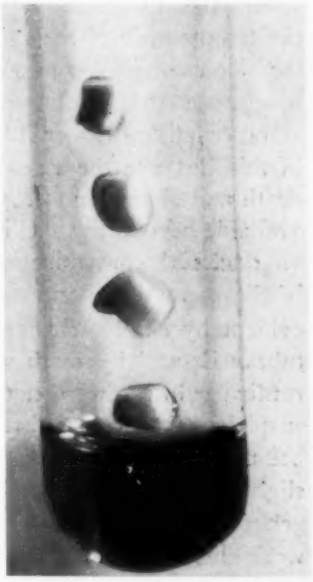


FIG. 4. — Tissue cultures showing tissue fragments in proper position and correct supernatant.

* Dog serum was used for the baboon and the pig vessels. The serum was centrifuged twice and stored in 2 cc. amounts at —20° to —25° C.

** Supplied by Dr. J. H. Hanks. Three to 5-inch beef embryos and an equivalent volume of BSS solution were mixed in a Waring blender for 1.5 minutes. The suspension was centrifuged for 30 minutes at high speed and the supernatant fluid collected and respun. The resultant fluid was tested for sterility and stored in small amounts at —20° to —25° C. Before use, the unfrozen material was re-centrifuged.

† Supplied by Dr. J. H. Hanks. Chicken blood was taken in a 10 cc. syringe containing 0.2 cc. of 10% sodium citrate, centrifuged twice, and stored in 1 to 2 cc. amounts in cotton-stoppered tubes at —20° to —25° C.

Some tissue cultures were photographed fresh, while others were fixed in Zenker's solution, cut at 3 to 5 mu., and stained with hematoxylin and eosine.

OBSERVATIONS ON VESSELS STORED BY THE VARIOUS METHODS

I. Tissue Preserved in 10 Per Cent Serum in BSS

Vessels stored within six hours following death (of animal or human) showed no consistent diminution in vitality due to this delay. Most of the tissue taken near six hours, however, grew less luxuriously than tissue taken within two to three hours. Variations in body size (of animal or human), the temperature of the room or icebox in which a body had been kept before the blood vessels were removed obviously presented factors which had a direct bearing on the viability of the removed tissues. The probability that vessel viability falls off rather sharply after death is supported by one human example; in this instance the vessels were obtained between 6½ and 7½ hours after death and showed no growth on tissue culture. Except for this, data are not available beyond the six-hour period.

Bacterial contamination is manifested by the appearance of cloudiness in the storage medium or by an abrupt change in its pH. It is also made evident by similar changes plus the growth of colonies in the tissue-culture tubes. Bacterial growth was not observed in stored dog tissue and although routine cultures were not taken, the culture of spun sediment from several suspicious flasks on various occasions yielded no growth. Human tissue stored before six hours was without demonstrable bacterial contamination. When slight cloudiness appeared after several weeks of storage, the spun sediment generally consisted of amorphous debris. In the one case where human vessels were obtained after six hours, cloudiness and demonstrable bacterial contamination became evident in each of eight flasks starting at 15 days. The contaminant (probably present when the tissue was first preserved) was *Ps aeruginosa*. Once it had made its appearance, it could not be suppressed with eight times the original antibiotic concentration.

In contradistinction to bacterial contamination, growth of fungi occurred sufficiently frequently (under 5 per cent) in stored dog tissue to constitute a nuisance, but was not observed in stored human tissue. Such contamination was generally not evident until three or four weeks of storage. Its appearance was unrelated to the type of stopper used. It was easily recognized by inspection of the flasks, all of which were immediately discarded.

The results of antibiotic titer tests were surprising and gratifying (Table I). Although the very high effective antibacterial activity cannot readily be explained, it probably results from the combined action of the specific agents, the serum, and possibly even the stored tissue. This high antibacterial titer, together with the low storage temperature, probably explains the very low incidence of bacterial contamination which was encountered.

Dog aorta maintained in cotton-stoppered flasks at 1° to 4° C. showed growth comparable to that of the fresh controls for approximately 20 days. After this time both the per cent of tissue pieces exhibiting growth and the

extent of growth apparently fell slowly, but substantial growth was demonstrated after storage periods of 50 days (Figs. 5 and 7). Tissue cultured during the first three weeks of storage frequently showed earlier and more luxuriant growth than the controls, suggesting a diminution of the usual adult growth inhibition.[28, 29] Tissues stored for more than three weeks generally exhibited a lag in the appearance of growth. For all storage intervals, the extent of growth paralleled the percentage of viable tissues.

Dog aorta stored at 6° to 11° C. in cotton-stoppered flasks grew more luxuriantly than that stored at 1° to 4° C. for two weeks but did no better at four weeks.

TABLE I.—*Antibacterial Titer of 10% Serum and BSS Storage Medium and Its Components*

Material Studied	Length of Use	Oxford Units/cc. Equivalent Penicillin Titer*	Mcg./cc. Equivalent Streptomycin Titer**
Dog serum	Fresh-frozen	0	640
Human serum	Fresh-frozen	0	640
BSS	Fresh	0	0
BSS plus dog serum	Fresh	0	640
BSS, dog serum, penicillin and streptomycin, (standard storage medium)	Fresh	1280 512	2000 6400
BSS, dog serum, penicillin and streptomycin, blood vessel	14 days	640	1000
BSS, human serum, penicillin and streptomycin, blood vessel	23 days	640	2000
	25 days	512	6400
	26 days	512	5120

* Assay organism *B. sublilis*, strain S.D.[26].
** Assay organism B. circulans[25].
The antibiotic assays were done according to the standard methods of the Food and Drug Administration.

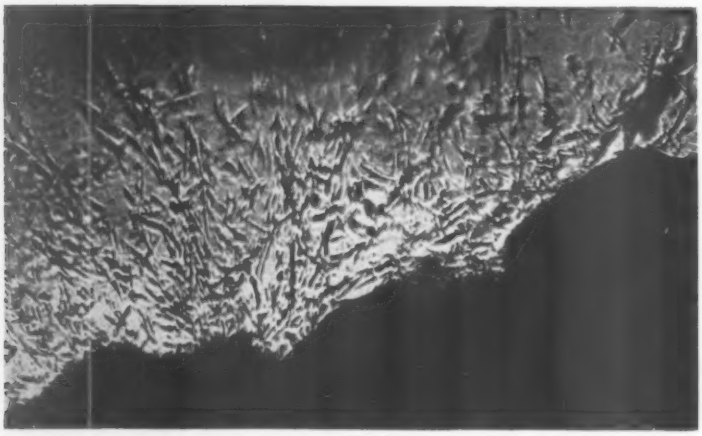
A smaller series of cultures of human vessels stored at 1° to 4° C. showed roughly comparable results (Table II, Fig. 6).

Pig and baboon aortas stored in 10 per cent dog serum and BSS maintained viability for about two weeks.

Renewing the nutrient medium in the storage flasks at two week intervals produced no definite growth improvement, and since it was shown that the original antibiotic titer was well maintained, the practice was discontinued.

In all of the cotton-stoppered series the storage of small (less than 1 cm.) portions of tissue alone adversely affected their chance of survival. Larger pieces of tissue produced an appreciable drop in pH of the storage medium within a few days to a week; the flasks containing only small tissue fragments at best maintained a constant pH but generally became more alkaline with time. Small fragments which had been stored alone regularly failed to show growth after short intervals. In order to give an overall picture, results obtained when small pieces of tissue were stored alone have not been excluded

FIG. 5



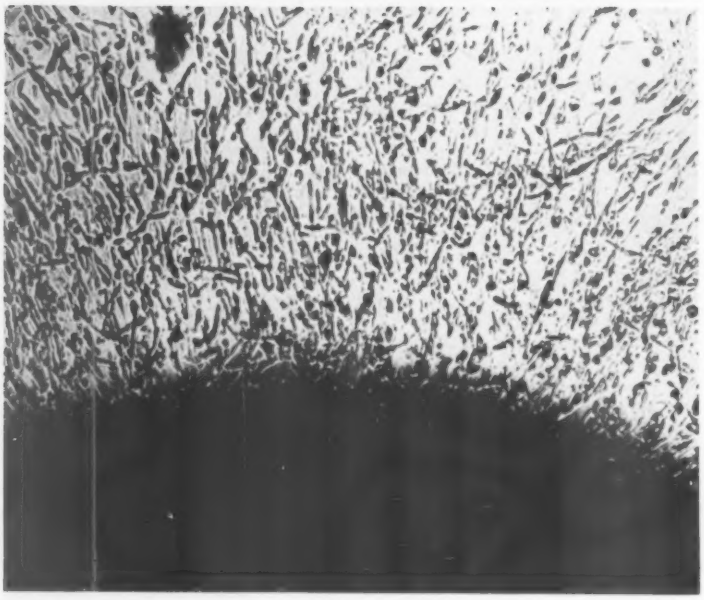


FIG. 6

FIG. 5.—Photomicrograph, unstained x55, of dog aorta tissue-culture. The aorta had been stored for 50 days in 10% homologous serum and BSS at 1° to 4° C. and had then been cultured for 7 days. There is active growth of fibroblasts.

FIG. 6.—Photomicrograph, unstained x55, of human aorta tissue-culture. The aorta had been stored 28 days in 10% homologous serum and BSS at 1° to 4° C. and had then been cultured for 7 days. There is active growth of fibroblasts.

TABLE II.

Results of tissue-cultures of human aorta stored in 10% serum and BSS at 1° to 4° C.
Three fresh controls showed 80% growth.
Each percentage represents studies on 8 pieces of tissue.

Duration of Storage	Percentage of Pieces Growing	
	Cotton-Stoppered Flask	Rubber-Stoppered Flask
1 day	75.	...
2 days	37.5	...
3 days	62.5	100
7 days	87.5, 0, 0	...
14 days	87.5, 12.5, 0, 0	100
16 days	37.5	100
21 days	75, 0,0	...
26 days	...	87.5
27 days	62.5, 0	87.5
36 days	25	...
37 days	...	75
42 days	0	...
49 days	0	...

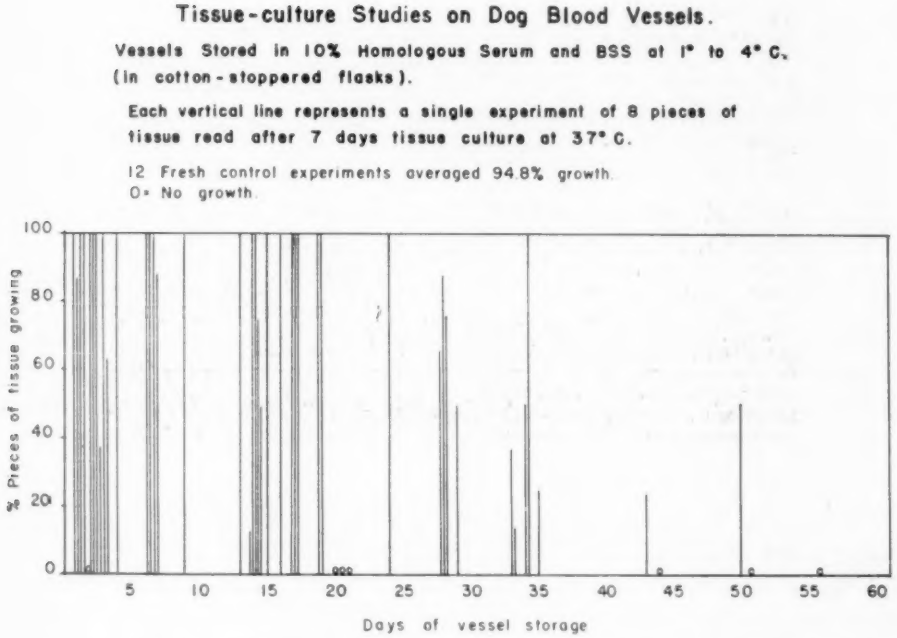


FIG. 7.—Results of culture of specimens of dog aorta which had been stored for varying periods of time. The vessels could be grown in a high percentage of cases after 35 days of preservation, and in one instance could be grown after 50 days of storage.

from Fig. 7 and Table II. A breakdown of some of the human data, however, shows how important this factor of small size is in influencing viability (Table III). For this reason, whenever it has been necessary to store small tissue pieces in cotton-stoppered flasks, the viability of the small piece can be enhanced by including a large piece of tissue in the flask.

TABLE III.—*Effect of Tissue Size on Survival. Blood Vessels, Human, Stored in 10% Serum and BSS at 1° to 4° C. as Large and Small Pieces and Then Cultured at 37° C. for 7 days.*

	Stored as Large pieces (3–4 cm.)		Stored as Small pieces (less than 1 cm.)	
Length of Vessel Storage	Number Pieces Cultured	Percentage Growth	Number Pieces Cultured	Percentage Growth
1 day	..	....	8	75.
3 days	..	....	8	62.5
7 days	..	....	24	16.
14 days	8	87.5	16	6.3
21 days	8	75.	16	0
28 days	8	62.5	8	0

TABLE IV.—*A Comparison of the Effects of Storage Temperatures and the Method of Sealing of Storage Flasks on Growth of Dog Arteries Preserved in 10% Serum and BSS. The Various Groups of Tissue-Cultures Were Carried Out Concurrently.*

Duration of Storage	Storage Temperature	Percentage of Pieces Growing	
		Cotton-stoppered	Rubber-stoppered
14 days (M)	1°–4° C.	100	100
17 days (L)		100	100
17 days (M)		100	100
17 days (S)		100	100
28 days (M)		62.5	100
33 days (L)		37.5	100
33 days (S)		12.5	100
44 days (M)		0	50
57 days (M)		...	0
17 days (M)	6°–11° C.	100	100
33 days (M)		Contaminated	100

Four fresh controls showed 100% growth.
Each percentage represents studies on 8 pieces of tissue.
L—approximately 6 cm. vessel segment.
M—2 to 3 cm. vessel segment.
S—1 cm. or smaller vessel segment.

In contrast to the results observed on tissues stored in cotton-stoppered flasks, blood vessels stored in rubber-stoppered flasks either at 1° to 4° C. or at 6° to 11° C. showed more reliable growth (Tables II and IV). When stored in rubber-covered flasks, the size of the tissue had very little effect on viability and in one instance 1 cm. sections of dog carotid artery grew as well after 33 days' storage as at 17 days. A cotton-stoppered control grew well at 17 days but very poorly at 33 days. The data on vessels stored at 6° to 11° C. is limited but indicates that this storage temperature is satisfactory.

Vessels in sealed flasks produced an appreciable drop in pH much more quickly than did similar vessels in cotton-stoppered flasks. Generally, the original pink color (pH 7.6) gave way to an orange (pH 7.2–6.8) within 12 to 24 hours. When this drop failed to occur, tissue-culture produced no growth. This early pH drop is therefore suggested as an important gross indication of viability. Once the pH had fallen to 6.8–7.2, it changed very slowly thereafter.

Blood vessels stored in 10 per cent serum and BSS were slightly yellowish in color, but showed no important edema. They retained their normal consistency and were indistinguishable from fresh vessels in suturing properties. Histological sections of tissue stored as long as 56 days showed preservation of architecture and cell detail (Fig. 8). Aortic grafts of stored tissue were generally successful; dehiscence and thrombosis rarely occurred (Fig. 9).

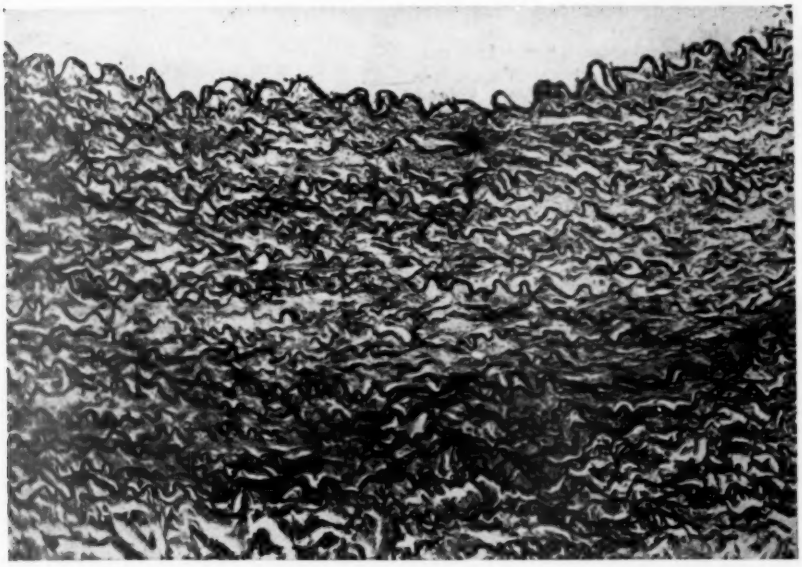


FIG. 8.—Section of stored dog aorta, showing excellent preservation of architectural detail. Hematoxylin and eosine. Vessel had been stored in 10% homologous serum and BSS at 1° to 4° C. for 56 days.

II. Tissue Preserved in Helium under Pressure at 0° C.

Tissue preserved by this method showed rapidly diminishing viability with no growth after one week and the segments were strongly acid in reaction indicating an excess accumulation of metabolites.

III. Vessels Preserved in Salt Solutions

Dog aortas held in BSS, normal saline, or "Ringer's" solution at 6° to 11° C. for periods up to four days grew almost as well as fresh controls.

After this time, there was a constant loss of viability and by 14 days' storage only a small proportion of the explanted tissue pieces grew. For this particular set of experiments, the normal saline was the most favorable and the "Ringer's" solution the least favorable storage medium.

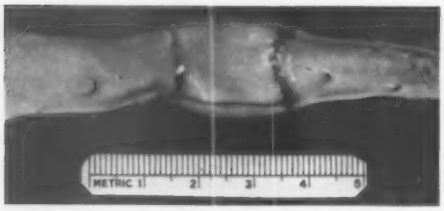


FIG. 9.—Graft of abdominal aorta (dog to dog). The grafted section had been stored in 10% homologous serum and balanced salt solution for 6 days and then had been implanted into a recipient animal which was kept for 6 months before sacrifice.

IV. Vessels Preserved in 100 Per Cent Serum

Tissue stored in whole autologous serum at 1° to 4° C. exhibited no growth or tendency to reduce the pH of the medium after three days' storage. Material stored for shorter periods was not studied.

TABLE V.—*Results of Tissue Cultures on Dog Aorta Stored in Serum Ultrafiltrate and Serum Ultrafiltrate with 10% Serum and BSS. Medium-sized Pieces of Tissue Were Stored.*

Storage Medium	Storage Temperature	Storage Time	Percentage of Pieces Growing: Cotton-stoppered	Percentage of Pieces Growing: Rubber-stoppered
Serum ultra-filtrate.....	1°– 4° C.	14 days	75.	...
		17	87.5	100
		29	62.5	...
		44	25	..
		57	0	...
	6°–11° C.	17	100	100
		33	...	100
Serum ultra-filtrate with 10% serum and BSS..	1°– 4° C.	14 days	62.5	...
		17	100	100
		29	50	...
		33	25	87.5
		44	37.5	...
		57	12.5	...
	6°–11° C.	17	100	100
		33	...	25

Each percentage represents studies on 8 pieces of tissue.

V. Vessels Preserved in Serum Ultrafiltrate

In general, dog vessels preserved in serum ultrafiltrate or serum ultrafiltrate plus 10 per cent serum showed growth roughly comparable to that obtained when 10 per cent serum in BSS was employed. The series of experiments was small and there were a number of variations but the impression was obtained that storage in 10 per cent serum in BSS was a little better. The addition of 10 per cent serum in BSS to the serum ultrafiltrate did not appear appreciably to improve growth. As with the earlier studies, however, sealing the flasks with rubber stoppers led to a distinct improvement in

viability of the stored tissue. The effect of the higher temperature, 6° to 11° C., was again to produce more luxuriant growth at about two weeks but little difference at four or five weeks. pH changes were comparable to those encountered with 10 per cent serum in BSS but the solutions tended to remain more alkaline. The results are compared in Table V.

VI. Vessels Preserved by Freezing

Material stored at —76° C. showed positive growth on tissue-culture in only two of 34 experiments.* In one instance the tissue was frozen rapidly (Method B) and in another it was frozen slowly (Method C). The growth was poor in both instances. Of 12 dogs who received frozen aortic grafts, all but two died because of thrombosis or breakdown of the graft. The tissue appeared to be more friable and more difficult to suture than fresh tissue. These results are unlike those reported by Blakemore[2, 3] and by Hufnagel.[16]

DISCUSSION

Although a graft of dead bone, cartilage, or blood vessel, may provide a suitable framework and produce a functional result[12, 13, 19, 20] the evidence at hand indicates that in the case of arteries, at least, more reliable results are obtained when living tissue is employed. Consequently, efforts have been directed primarily to finding a method of preserving vessels in a viable state. Several modes of storage, including freezing, have been abandoned by us at least temporarily, since, when employed, viability could be demonstrated only sporadically and, in experimental animals results from grafts were poor. The method of storage recommended in this paper is not entirely new but is based on the previous work of many others.

Bert[1] refrigerated rats' tails in confined air at about +12° C. for several days and then successfully transplanted them. Carrel[6, 8] stored blood vessels, skin, fascia, and other tissues, in vaseline, moist air, normal saline, and "Ringer's" solution, at temperatures slightly above freezing. He evaluated his method of preservation after one to six days by cultivation of stored embryonic tissue and after intervals as long as seven weeks by grafting stored adult tissue in animals. The maximum duration of cell viability was not determined. Lambert,[17] Lewis and McCoy,[22] Hetherington and Craig,[15] Waterman,[32, 33] Walter *et al.*,[31] Hanks and Wallace,[14] Garry,[10] and Carpenter,[5] studied the survival of refrigerated embryonic and other tissues by tissue cultivation or oxygen consumption, but were either unable to demonstrate viability after more than short intervals or were concerned with comparatively brief periods of storage. Their work indicates that refrigerated tissue retains its viability for varying periods of time, depending primarily on the type of tissue,[32, 33] and secondarily on the size of tissue pieces,[22] available oxygen,[10, 14, 24] storage temperature,[15, 22, 33] and other factors. Irreversible changes took place quickly

* Tissue refrigerated but not frozen in the copper tubes grew well on tissue-culture, indicating that the presence of the metal itself did not account for the failure of the frozen tissues to grow.

in brain, kidney, liver, and other solid organs, while bone, cartilage, skin, fascia, and blood vessels, survived for comparatively long intervals. The degree of preservation was more or less dependent on the size of the fragments, very small pieces of tissue surviving for only brief periods. Oxygen demand was greatly diminished as the temperature fell. Tissue fragments at 37° C. required very high oxygen tensions to prevent necrosis,[24] while at 0° C. tissues were able to survive for a time even when oxygen was excluded.[10, 14]

Tissues for clinical grafting have been stored refrigerated for short intervals. La Roe[18] kept skin in "Tyrode's" solution for periods of one week, while Castroviejo[9] stored corneas for two to five days in "Ringer's" or normal saline. Both reported satisfactory clinical results. More recently, Matthews[23] preserved human skin wrapped in saline sponges, in air-tight containers at +3° to 6° C. He reported viability after eight days as measured by tissue cultivation, and stated that autogenous grafts at three months were successful.

It is thus clear that certain tissues can be preserved vitally by simple refrigeration. However, evidence concerning the limitations of storage methods is slowly accumulating. Skin[14] and blood vessels (present report) can be preserved alive for about a week in the absence of a buffered environment by storing at 0° C. with the exclusion of oxygen. As shown both by these workers and ourselves, however, there is an unfavorable accumulation of acid metabolites and a rapidly falling viability. Tissue stored in such media as balanced salt solution, Ringer's solution, or normal saline, at temperatures just above 0° C., will also remain alive for short periods, as demonstrated by our data, but the lack of suitable nutrient material is evidently unfavorable for lengthy preservation of viability. In addition, blood vessels so kept may become edematous and prove unsuitable for vascular grafts after as little as 24 hours' storage.[11] Preservation in serum or whole blood is also satisfactory for short periods of time,[14] but the large protein and fat molecules seem seriously to interfere with metabolism.[29] The preservation of tissue in 100 per cent serum was unsuccessful in one series of experiments performed by us.

Thus, it appears that an ideal storage medium should contain a physiological concentration of salts, buffer, glucose, and the small accessory molecules which are present in serum. The large protein and fat molecules should probably be in reduced concentration. The storage medium developed by Hanks and Wallace[14] fulfills these criteria. It was found by them to be entirely suitable for storage of rabbit skin for periods up to two weeks at 8° C. Their procedure was modified in our hands by employing somewhat lower temperatures and by the more liberal use of storage medium.

The use of serum ultrafiltrate as a storage medium is suggested by the above reasoning, since all of the large molecules have been removed from it, while the small molecules remain. The data accumulated to date indicates that this solution either alone or with 10 per cent serum is satisfactory but is not superior to 10 per cent serum in BSS.

In the early part of the work cotton stoppers were used in the storage flasks because we thought it was important to facilitate the metabolic exchange

of the blood vessels which was evident even at low temperatures. This proved fairly satisfactory except in the case of small vessel segments which retained viability for only relatively short periods of time.* Experiments conducted with tightly-stoppered flasks showed that the metabolic activity was not sufficient to require a free exchange of carbon dioxide and oxygen. In addition, it was found that small vessels preserved in this latter manner remained viable as long as did large ones. Consequently, tightly-fitting stoppers are now used routinely.

The present study indicates that blood vessels may readily be preserved alive and with normal physical properties for periods of at least seven weeks. They have been safely employed in dogs and humans during that time for homoplastic grafts. Proper exploitation of this method should improve the surgical treatment of coarctation of the aorta, Tetralogy of Fallot, arterial aneurysm, injuries to major vessels, *etc.*

The general method of storage with suitable modifications might be applicable to fascia, skin, bone, nerves, cartilage, and corneal tissue.

SUMMARY

The vital storage of vascular segments in 10 per cent serum and a balanced salt solution at temperatures slightly above freezing is described. The temperature of storage is not critical. The method is simple enough to be readily useful. Viability of the tissue is readily shown by growth in tissue-cultures after storage for as long as seven weeks. The preserved segments closely resemble fresh vessels in physical qualities, and a large series of successful grafts in dogs has been completed. Vessels have also been collected from humans, stored, and have been employed successfully for alleviation of the Tetralogy of Fallot and in treatment of coarctation of the aorta. This method of blood-vessel preservation appears superior to any other yet tried by us, including freezing. The theoretical basis for the storage method is discussed.

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THE MEDICAL AND SURGICAL TREATMENT OF HYPERTENSION*†

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This presentation deals with the present day management of arterial hypertension as practiced by the medical and surgical staff of the Stanford University School of Medicine.

In certain patients the etiology of hypertension is known, such as in the condition of coarctation of the aorta, or of cortical or medullary tumors of the adrenal gland, or renal disease including unilateral renal lesions and glomerulonephritis, but in the majority of patients the etiology of essential hypertension is not definitely known. Heinbecker's[1] humoral hypothesis, that hypofunction of the neurohypophysis sensitizes the blood vessels to a variety of pressor substances such as renin, epinephrine, and progesterone, may prove to be important. Goldblatt[2] has recently summarized the evidence which has led him to believe that essential hypertension is of renal origin. In general two views are currently held: some authors feel that the arteriolar vasoconstriction with resultant hypertension can be the result of increased sympathetic impulses, while others believe it may be caused by a circulating humoral substance.

In its early stages essential hypertension has no organic changes; one finds only an elevated blood pressure which varies from time to time and may exist for years or even for decades with no serious symptoms and, in some individuals, with but little shortening of life.[3] In the advanced stages of this condition peripherally constricted arterioles develop that are at first functionally spastic and then later become organically damaged, manifesting such constriction by cerebral, retinal, cardiac, or renal complications. When these symptoms appear more or less simultaneously the syndrome is known clinically as malignant hypertension (usually "essential," but sometimes with a recognizable cause). Then life expectancy is brief, the majority of patients dying within two years, with an average length of life after diagnosis of about eight months.[4]

In patients with essential hypertension, as in those with peptic ulcer and probably in those suffering from angina pectoris, certain emotional and physical reactions are more intense and frequent than in healthy people of the same age. The predisposing personality of the hypertensive patient may be present in early life and is not the result of unusually high blood pressure nor

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the result of secondary vascular disease.[5] This hyperactive reaction to environmental stimuli may be of physical or endocrine origin, and once recognized can be treated by the internist with very mild sedation and by explanation to the patient of his particular reactions so that he will follow suggestions with confidence. Generally the headache, dizziness and marked tenseness and nervousness can be and should be treated by removal of "environmental difficulties or adjustments to them,"[5] supplemented by suggestion and by sedation.

Even a brief survey of the published results after sympathectomy for hypertension reveals a lack of agreement regarding the selection of cases. At one extreme are those who would operate upon symptom-free youths with diastolic levels of 90–100 mm. Hg, in the hope that future progress of the disease will be prevented. The most contradictory view is held by those who recommend operative procedures only for patients with the very worst malignant hypertension, refractory to medical management. We subscribe to neither philosophy: not to the former, because we as well as many others have seen patients with essential hypertension who have continued in their work without persistent symptoms for 20 and 30 years before organic changes in the arterioles have led to trouble, and because we have seen hypertensive disease progress despite sympathectomy done early in youth; not to the latter, for then operative risks are great and results unsatisfactory in actual experience. In our intermediate position, sympathectomy is recommended when danger signals appear in the patient with high diastolic pressure levels: when his pressure rises even higher, when his symptoms become very severe, and especially when vascular complications (particularly those threatening the eyes) become demonstrable. Ignoring most of the published contraindications, we have recommended and performed operations with no arbitrary age limit and in spite of cerebral and coronary arterial occlusions, recent congestive heart failure, and even chronic glomerulonephritis. It appears that our patients have in general been subject to much more severe hypertensive disease than those described by most authors.

"Sympathectomy is a palliative and not a curative measure. . . . Helpful and even life saving though sympathectomy is to some patients, at present it fills only a small gap in the great therapeutic problems of essential hypertension."[6] We agree with these words of Fishberg and with his estimate that sympathectomy and splanchnicectomy are indicated in only a very small proportion of patients with essential hypertension.[6]

Special attention will be given elsewhere[7] to the chronic glomerulonephritic patient with hypertension. Although usually considered as too bad risks for surgery and thought not to respond, a few patients with advanced renal disease with azotemia have been operated upon with results considered worthwhile since they received relief from incapacitating and intolerable symptoms. Ten such patients had the one stage bilateral transdiaphragmatic splanchnicectomy and sympathectomy. Two could not be followed after operation and one died in the immediate postoperative period. Of the re-

maining seven, two died from uremia after five and eight months of freedom from their severe preoperative symptoms and the other five patients have remained asymptomatic for periods ranging from three to 49 months.

The surgical experience with splanchnic and sympathetic resection for severe hypertension and vascular damage in approximately 130 patients in this report extends over 13 years beginning in 1935. We have realized throughout this period that we were attempting surgically to help a symptom, namely high blood pressure, and were in no way seeking a cure of the cause of hypertension.

Our operative procedure has always been one stage with two operators working simultaneously, since the unilateral operation has very little effect upon the blood pressure. The one-stage operation, lasting a little over an hour, always is easier on the patient, because there is not the waiting period nor the hazard of a second operation and a second anesthesia. The Peet[8] procedure of supradiaphragmatic resection was done until February 1942 when a modification of the Smithwick[9] operation was developed. In some recent cases with rapidly failing vision, retinal hemorrhage and papilloedema, bilateral sympathetic denervation of the head by removal of T_2 and T_3 sympathetic ganglia through a separate transverse incision has been done at the beginning of the bilateral thoracolumbar resection.

The results in the first 40 patients operated upon from 1935 to 1938 by the Peet procedure have been published in 1940.[10] We now wish to present the status of these same patients as determined in 1947-1948. There was a 20 per cent mortality within the first two weeks chiefly through failure to maintain adequate operative and postoperative arterial pressure. (It was about 1940 that neosynephrine was first used routinely to prevent renal and cerebral ischemia.) Sixteen patients (40 per cent) died of hypertensive disease in from two weeks to two years after operation; only three or four of these had even transient symptomatic improvement. Five patients (12.5 per cent) could not be traced and of these three or four are probably dead; four had shown no postoperative improvement up to five years, and one patient's headaches were relieved but his pressure levels had already exceeded the postoperative maximum 20 months after operation, beyond which time he could not be followed. Six additional patients (15 per cent) are known to have died of hypertensive disease four, six, six, ten, ten, and 11 years after operation, some following shorter periods of symptomatic improvement; three of these were included in the group with the best results, including an appreciable fall of blood pressure, when the first postoperative study[10] was made.

Only five patients (12.5 per cent) are known to be living, at 9–12 years after operation. In each, the blood pressure is now at or above the preoperative level. One of these (Mrs. G. in Table 3 of reference 10) had never shown improvement; in one (Case 4 of reference 10) the symptoms of fulness in the head and markedly pulsating arteries were alleviated without reduction of pressure; in three (Cases 6–8 of reference 10) objective improvement had been found for several years.

Neither enough time had elapsed nor adequate data acquired to warrant a report on all of the remaining patients. Without further conscious selection, however, the present state of fifty patients operated upon from 1938 to 1946 may be given.* There were only three postoperative deaths (6 per cent), but 21 others (42 per cent) died of their disease between two weeks and two years after operation. An additional six (12 per cent) died of hypertensive complications about four years postoperatively. Nine (18 per cent) appeared

TABLE I.—*Results of Splanchnic and Sympathetic Resections in Ninety Hypertensive Patients.*

Status in	40 Operations 1935–1938 1940 Per Cent	1947–48 Per Cent	50 Operations 1938–1946 1947–48 Per Cent
Died in 2 weeks	20	20	6
Died in 2 years	27	40	42
Died later	..	15	12
Not followed	..	12.5	..
Unchanged	23	2.5	18
Symptomatic improvement	15	10	18
Pressure reduced	15	0	4

to be unchanged, and an equal number obtained symptomatic but not objective relief. In only two patients (4 per cent) does the pressure remain appreciably lower, after one and one-half and six years. This is not the entire story; rehabilitation and fall in pressure levels were very gratifying in three patients (6 per cent) for two to four years prior to relapse, with subsequent death in two.

Table I outlines the above findings briefly. If statistics as a whole mean anything, these results may seem not to compare favorably with those of others. We wish to point out again, however, that the patients selected for operation generally suffered more hypertensive disease than those usually described by other authors.

For the type of patient referred to us for resection we feel the operative procedure is adequate and that total sympathectomy would not alter the statistics as presented. We are in accord with Heinbecker[11] that probably "the only two organs capable of releasing humors concerned with the pathogenesis and symptomatology of hypertension and whose function can be modified by sympathectomy are the kidneys and the adrenals." Anatomic studies of the innervation of the kidney and adrenal glands show that the nerves pass from the celiac ganglion and the upper two lumbar ganglia so that removal of the splanchnic nerves and the sympathetic chain from T_9 or T_{10} through L_2 ganglia should effectively denervate the kidneys and adrenals.

We have modified the Smithwick operation by extending the Peet approach. Bilateral paravertebral incisions are made by two surgeons working as a team and the operation is carried out simultaneously on both sides (Fig.

* More than 80 per cent of the operations were performed in 1941–1945.

1). The long back musculature is divided and segments of the 11th and 12th ribs are resected from the transverse processes laterally for 4 to 5 cm. (Fig. 2). The intercostal muscle bundle and vessels are resected leaving the intercostal nerve intact as the long brain spatulae are now used for retracting the pleura without trauma to the nerve (Fig. 3). The pleura is pushed away from the vertebral bodies. The outer crus of the diaphragm is pushed off or separated

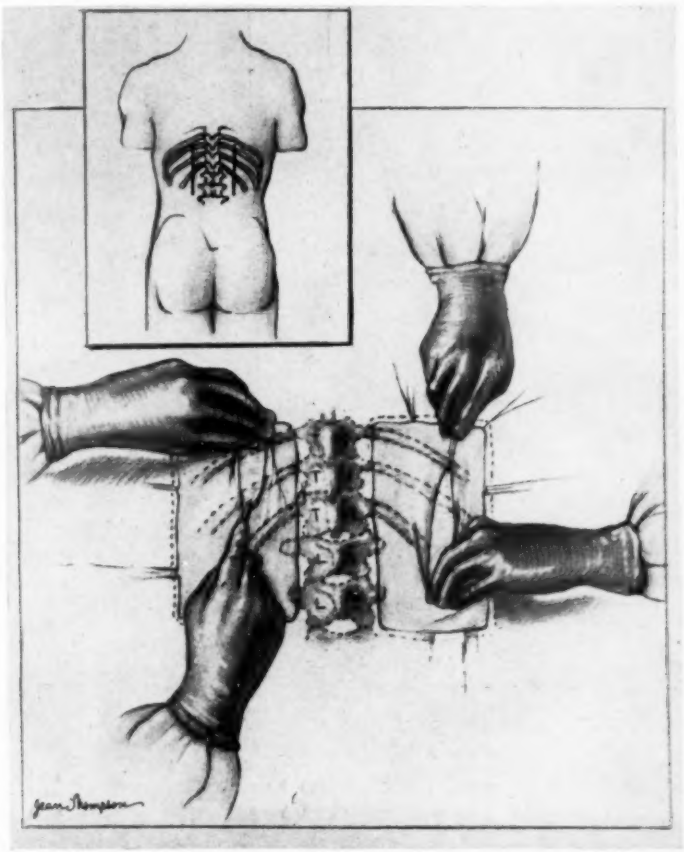

FIG. 1.—Position of patient, and of incisions being made by two operators working simultaneously in performing the one stage bilateral transdiaphragmatic splanchnicectomy and sympathectomy.

from the body of the 1st lumbar vertebra and the diaphragm is split in the direction of its fibers for 3 to 4 cm. for palpation and if necessary inspection of the adrenals and upper poles of the kidneys. The retropleural space is freed upward to the level of the 8th or 9th rib and the sympathetic chain, splanchnic nerves and the branches to the aorta on the left side are mobilized (Fig. 4). The sympathetic fibers are followed downward in the retroperitoneal space until the 2nd lumbar sympathetic ganglion is located. The chain is divided below this ganglion and then above, usually between the 8th and 9th thoracic ganglia. The greater and lesser splanchnic nerves are resected from the 8th

or 9th rib down to and including the upper half of the celiac ganglion. Ordinarily the patient receives 500 cc. of whole blood during the operation. Neosynephrine is administered by the anesthetist as it is necessary to maintain at all times an adequate blood pressure during and following the operation, using 0.1 cc. intravenously or 0.2 to 0.4 cc. intramuscularly of a 1:1000 solution.

The blood pressure may fall precipitously to dangerous levels during and

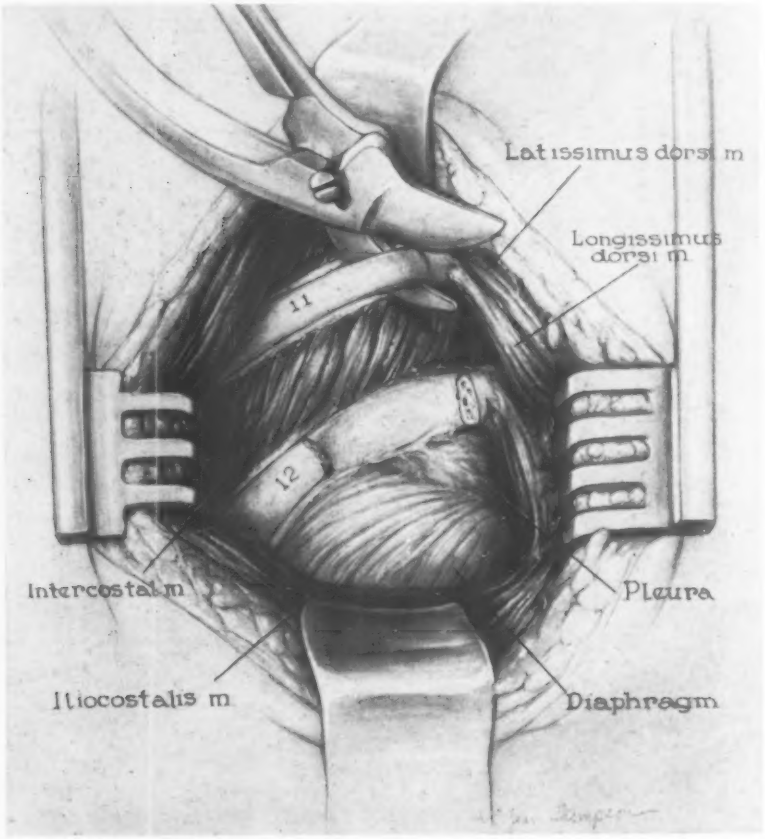

FIG. 2.—Exposure of 11th and 12th ribs, pleura and diaphragm with resection of the inner portions with transverse processes of 11th and 12th ribs.

after a one stage splanchnicectomy and sympathectomy if special efforts to maintain it are not employed. Shock, cerebral anoxia, and renal ischemia are the principal dangers, the latter complications being of particular importance in patients with advanced renal disease. Blood pressure measurements are made every 5 to 15 minutes during the first postoperative day and less frequently thereafter as is indicated. If the blood pressure falls below 140 over 100, neosynephrine is administered. It may be necessary at times to continuously infuse neosynephrine diluted with 5 per cent glucose in distilled water.

Maintenance of an adequate fluid balance is necessary and is of the utmost importance in patients with advanced renal disease and azotemia. If dehydration and salt depletion occur it may be difficult to sustain the blood pressure at desired levels, the azotemia may be intensified and acidosis may ensue. Administration of excess salt and water may result in edema and heart failure.

The 24-hour urine volume and quantity of sodium chloride excreted is measured daily in those patients with severe renal lesions. The total fluid

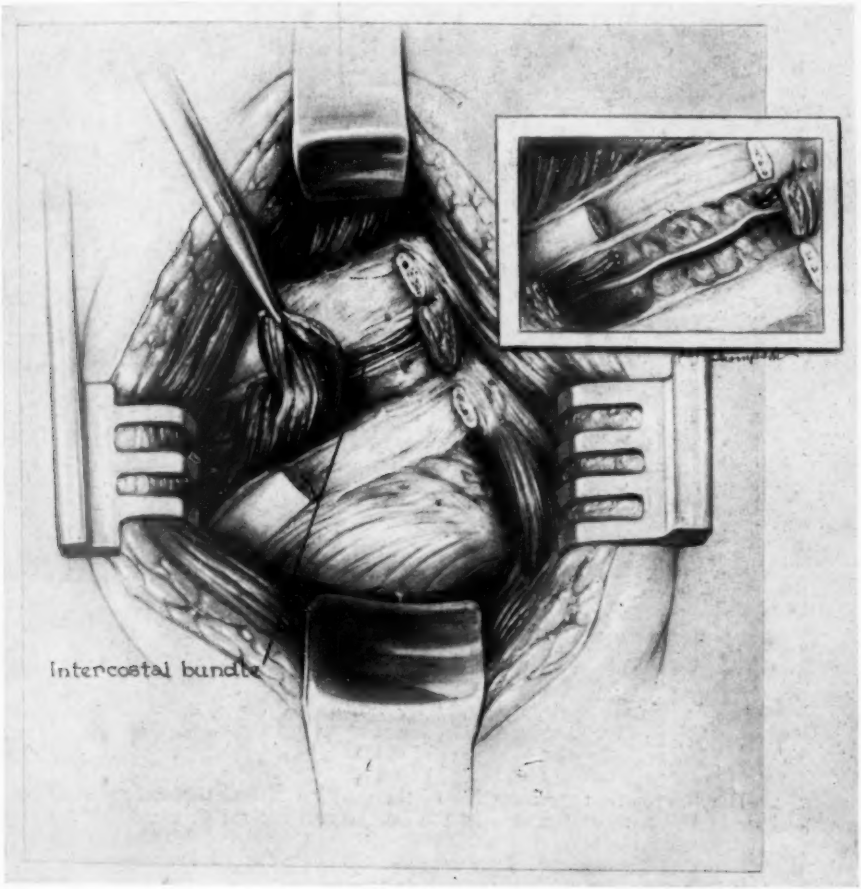

FIG. 3.—Removal of muscle and vascular bundles between beds of 11th and 12 ribs leaving 11th intercostal nerve intact.

intake and output is also measured. Fluids should be given slowly and cautiously, usually about 2000 cc. daily in excess of that lost by vomiting. Since little or no salt is lost in the urine, only enough to replace that lost by sweating and vomiting is needed.

Unless an adequate number of calories is supplied, body protein will be used for energy, deamination of amino acids will be increased, and the azotemia may be intensified. Intravenous solutions should contain glucose of 5 to 10

per cent, the patient should be urged to consume food and fruit juices with sugar as early as possible after operation. When food can be eaten without difficulty, an adequate low protein diet is given.

Following operation intercostal neuralgia of varying degree develops even if the intercostal nerves are divided. Seconal and nembutal are of help for this condition which lasts from one to several weeks and causes fluctuation in the postoperative blood pressure.

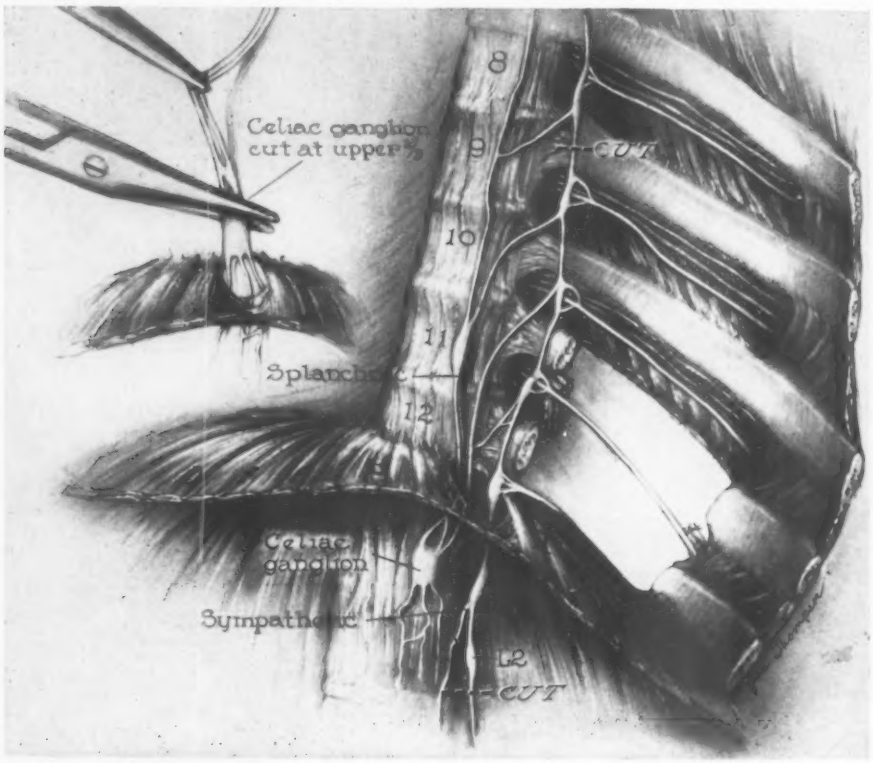

FIG. 4.—Diaphragmatic representation of the position of and the amount removed of the splanchnic and sympathetic nerves in the one stage bilateral thoracolumbar splanchnicectomy and sympathectomy.

Usually in the second week when tension has subsided the patient's mode of life and work is discussed and adjustments planned not only with the patient but with his or her family. The proper reaction of the patient to the environment is most important in seeking a successful outcome from the operation, and the surgeon should be of great aid to the internist in securing this adjustment. We are in accord however with Ayman's[5] statement that essential hypertension still is a medical disease which should be studied primarily by the internist whose experience is obviously much greater than that of the surgeon in the evaluation of cerebral, cardiac, and renal functions. The postoperative evaluation should also be primarily in the hands of the internist.

SUMMARY

Essential hypertension is fundamentally a disease which in the great majority of our patients has been adequately treated for years and for decades by the internists of the Stanford University School of Medicine.

After long medical treatment certain few patients no longer respond favorably because of the development of malignant hypertension, or because of renal, cerebral or cardiac complications of essential hypertension, or because the glomerulonephritic case with hypertension enters into the terminal stages.

Such patients, although considered unsatisfactory for operation by most surgeons, are recommended for the one stage bilateral transdiaphragmatic splanchnic and sympathetic trunk resection in which procedure two surgeons operate simultaneously.

With proper operative and postoperative attention to maintenance of an adequate blood pressure at all times, the immediate mortality has been about 6 per cent.

Such patients referred for operation are given continued and careful supervision by the internist immediately after the operation to prevent cerebral anoxia and renal failure.

This operative procedure affords a minimal surgical strain on such patients and is considered worth while because it offers temporary symptomatic relief in about one-fifth of the referred cases.

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CONTROL OF HEMORRHAGE FROM WOUNDS OF THE CORONARY VESSELS BY THE GELATIN SPONGE PATCH TECHNIC*†

An Experimental Study

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THE ABSORPTION[1] and hemostatic action[2] of gelatin sponge has been the subject of several previous communications. In experimental resections of the liver the control of hemorrhage with gelatin sponge has been obtained by the "blanket" technic and in wounds of large veins by the "patch" method.[3] In experimental wounds of large arteries the hemorrhage has been controlled by a "cuff" of dry compressed gelatin sponge supported by a chromic catgut sheath.[4] In experimental wounds of the auricles[5] and ventricles[6] the gelatin sponge "patch" was found adequate to control massive hemorrhage from the heart.

The application of these experimental studies to the problems of hemostasis in general surgery has been outlined[7] and clinical observations on the use of gelatin sponge in patients has been presented.[2, 8, 9] It has been pointed out that the indications for the use of gelatin sponge or any other hemostatic agent in clinical surgery should be limited to the control of hemorrhage where ligature or suture was not adequate, desirable, or feasible.

Hemorrhage from wounds of coronary vessels appeared to present a particular challenge in hemostasis, in that the vessels are too small and in too rapid motion to permit suture of the wound and the sequel of myocardial infarction too hazardous to permit ligation of the vessels, especially the artery. Although hemorrhage from wounds of the coronary vessels may be encountered rather infrequently, nevertheless they do occasionally occur as a result of trauma, pericardiocentesis, or in the course of a pericardiectomy.

This experimental study was undertaken to determine the feasibility of utilizing the gelatin sponge "patch" technic to meet this particular clinical problem of hemostasis, as well as to evaluate the effectiveness of this hemostatic agent by a more critical experimental test than has heretofore been carried out.

EXPERIMENT

The dogs were anesthetized with Nembutal using 33 mg. per kilogram of body weight. A tube connected with an adjustable positive pressure air valve

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† This work was aided by a grant from the Upjohn Company, to the University of Illinois College of Medicine.

was introduced into the trachea. With aseptic technic, an incision was made on the left side of the thorax entering the pleural cavity in the 4th interspace. The degree of lung expansion was regulated by immersing the air outlet tube from the closed mask in a 5 gallon jug of water. The pericardium was opened and special care was taken to avoid torsion and kinking of the base of the heart. A wound was made with a scalpel in the anterior descending branch of the left coronary artery and vein producing a copious hemorrhage which had enough force to carry the stream of blood 3 to 4 feet. (See Fig. 1.) It is believed that in some instances the scalpel wound completely transected

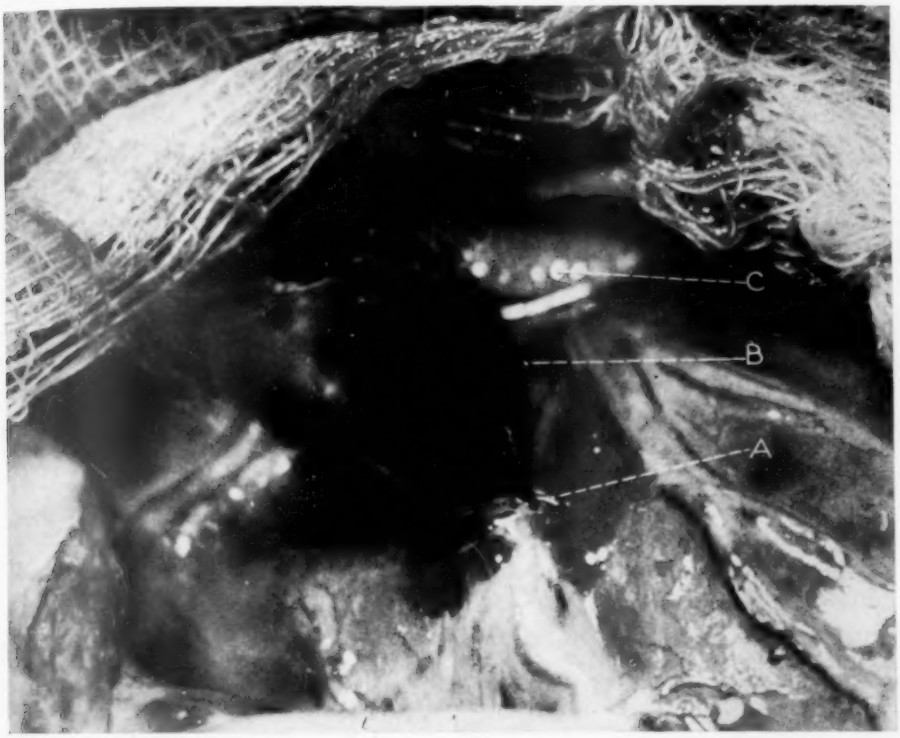

FIG. 1.—Showing hemorrhage from scalpel wound of coronary artery and vein. A—incision in wall of artery and vein. B—the massive spurt of blood through the incision. C—tip of auricle.

the artery, although in most instances a partial transection was undoubtedly obtained. In the first five experiments the wound was made in one of the major terminal branches. In the remainder of the experiments the wound was placed proximal to the major terminal bifurcation in the upper third of the artery just medial to the tip of the left auricle. The "patch" of gelatin sponge was prepared from the commercially available product "Gelfoam" size 100 which is provided sterile in sealed packages. The gelatin sponge was first compressed by the fingers and then a piece about 1 inch square cut out of the larger compressed sheet. These "patches" of dry compressed gelatin sponge

were applied over the bleeding wound in the vessels and held in place with the fingers for 10 to 20 minutes. In most instances it was found necessary to use as many as four or five successive patches before the hemorrhage was completely controlled. An additional reinforcing patch was usually necessary. In using the dry compressed gelatin sponge there is a tendency for the sponge to stick to the gloves, so that in removing the finger pressure from the patch, dislodgment occurs. This was obviated in these experiments by first letting one side of the sponge become soaked in blood and then turning it over, using pressure of the gloved fingers on the outer blood soaked side.

The gelatin sponge patch technic was used in 37 experiments in which wounds were produced in the coronary artery and vein. In four other control experiments oxidized cellulose was used. In addition there was a control series of two animals in which the coronary vessels were ligated after transection. In two animals a blood soaked gelatin sponge patch was inserted into the pericardial cavity without producing a wound of the vessel. These latter two experiments were done as controls for the electrocardiographic studies which were made on most of the animals before, during, and after the wound of the vessel was produced or the vessels ligated.

The animals which survived the experiment were sacrificed at varying periods of time from one week to six months after the wound was produced. Photographs were taken of the heart and arteriograms were made of the left coronary artery, using either red lead or metallic mercury. Several of the hearts were prepared as cleared tissue specimens and in the remainder the area where the wound had been produced was cut out and prepared for microscopic study.

RESULTS

In the series of 37 experiments in which a gelatin sponge patch was used as the method of attempting control of hemorrhage from scalpel wounds of the anterior descending branch of the left coronary artery and vein, the following results were obtained:

In three experiments, ventricular fibrillation and cardiac arrest occurred before the hemorrhage could be controlled by the gelatin sponge patch. In one of these, death occurred shortly after the wound was made in the vessels. In two experiments death occurred 35 minutes to one hour afterwards, and represents a definite failure to obtain hemostasis by this method.

In four experiments, the hemorrhage was controlled by the gelatin sponge patch but ventricular fibrillation and cardiac arrest occurred shortly afterwards. In two this occurred before closing the pericardium; in one it occurred while the chest wound was being closed; and in one other it occurred after the chest was closed, the fibrillation being detected by the electrocardiogram. On reopening the chest this was substantiated and attempts at defibrillation failed.

In one experiment, the hemorrhage was controlled by the patch but the animal died shortly after the chest was closed, apparently as a result of the anesthesia.

In two experiments, the animal died some time during the night after the operation and at autopsy were found to have a hemopericardium due to dislodgment of the patch and secondary hemorrhage.

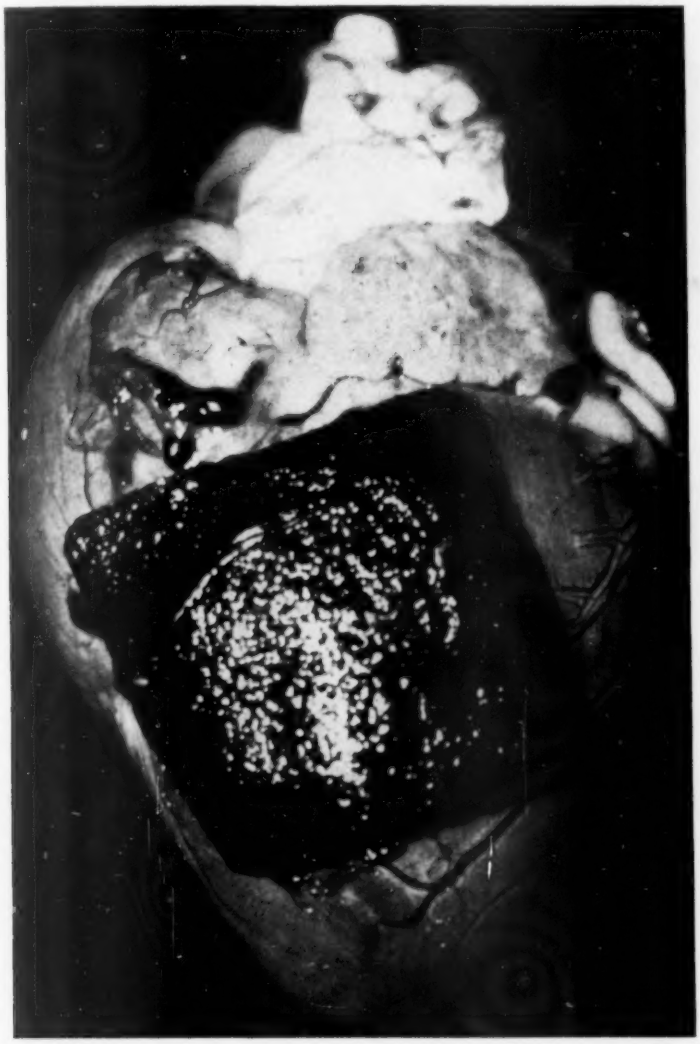

FIG. 2.—Showing gelatin sponge patch covering wound of the coronary vessels. The control of the hemorrhage is apparently due to the clotting of the blood in the interstices of the sponge which produces essentially a "reinforced clot," the gelatin sponge furnishing the structural support. This "reinforced clot" seals off the wound in the vessel, prevents further loss of blood, and permits restoration of blood flow in most instances until healing occurs.

In one experiment, the animal died some time during the night after the operation and at autopsy 20 cc. of blood was found in the pericardial cavity, although the sponge was adherent to the wound in the coronary vessels. This

amount of hemopericardium may have contributed to the impairment of cardiac function but did not seem to be the sole cause of death, which was probably due to myocardial changes as a result of impairment of circulation after cutting the vessels.

FIG. 3.—Showing gelatin sponge patch one week after application to wound of coronary vessels. The patch is moderately adherent to the visceral and parietal pericardium and firmly adherent to the area where the wound was produced.

In 26 experiments, the hemorrhage from the wound in the coronary vessels was controlled by the gelatin sponge patch technic and the animals survived the experiment. (See Fig. 2.) The number of patches required to obtain hemostasis varied from one to nine and usually at least one reinforcing patch was necessary. In most of the experiments at least four or five successive patches

were used before the bleeding was adequately controlled by a final reinforcing patch.

One animal died after two days from pneumonia and one after a week as a result of massive infection in the chest incision. The remaining 24 animals were sacrificed at varying periods of time from one week to six months after

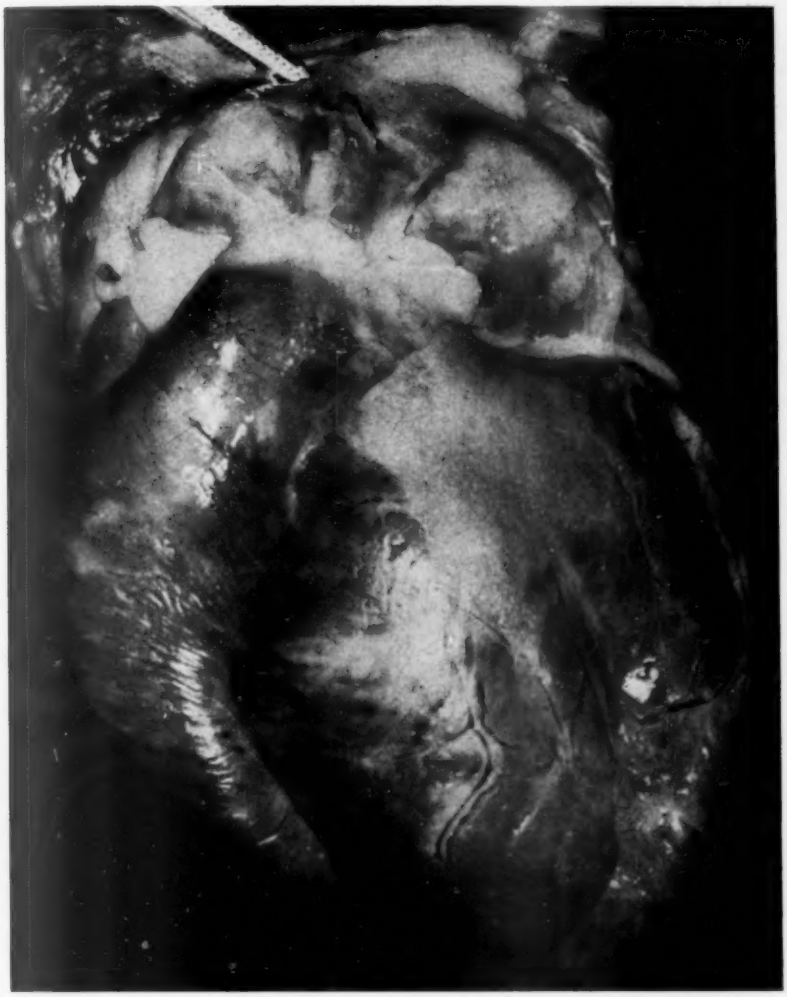

FIG. 4.—Showing gelatin sponge patch six weeks after application to wound of coronary vessels. The patch has thinned out considerably due to absorption and is so adherent to the heart that it cannot be removed except by sharp dissection.

the wound was produced. The length of time before sacrificing was as follows: two at one week, two at two weeks, two at three weeks, one at four weeks, one at six weeks, three at two months, two at two and one-half months, five between two and one-half and three months, two at three months, one each at three and one-half, four and one-half, five and six months.

The condition of the gelatin sponge at autopsy varied according to the length of time it had been implanted. During the first few weeks the sponge was red in color and became increasingly firm. It was only moderately attached to the visceral pericardium during the first week by thin transparent fibrinous adhesions as well as to the parietal pericardium. The sponge remained rather firmly adherent, however, to the area where the wound was

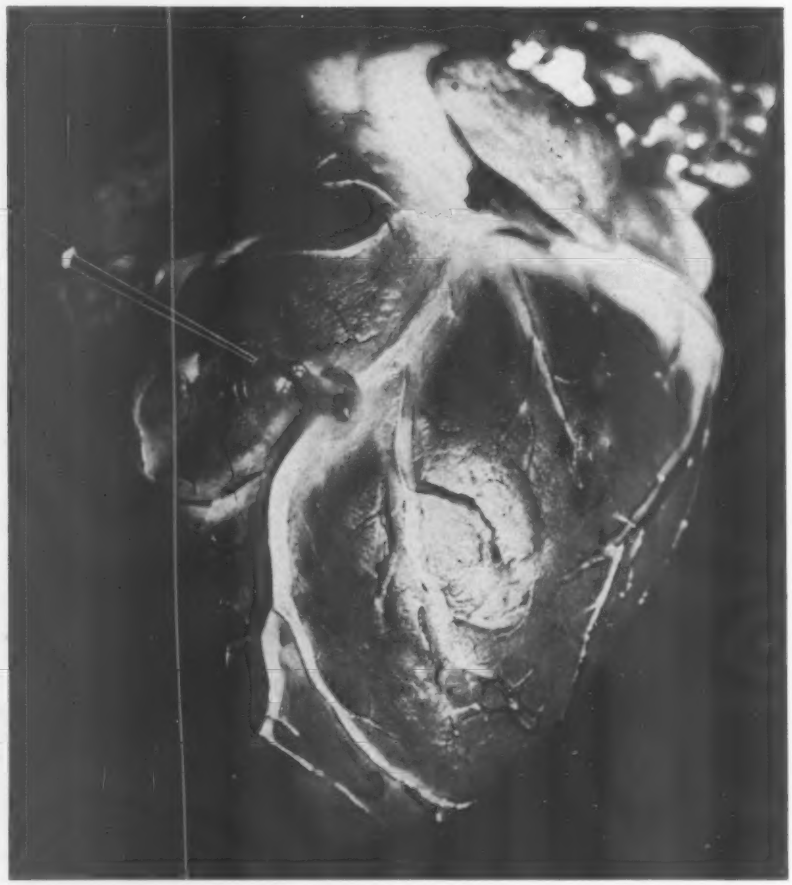

FIG. 5.—Showing condition of coronary vessels 12 weeks after patch of gelatin sponge applies to wound. The gelatin sponge has been completely absorbed and replaced by a small fibrous plaque which covers the area where the wound was produced. Arteriogram demonstrates patency where the wound was produced.

made and could not be separated from this region without tearing the sponge. After one week the sponge became increasingly adherent to the visceral as well as parietal pericardium (See Fig. 3) and after three weeks the sponge tended to split when the pericardial sac was removed, leaving a portion of the sponge adherent to both structures. After four weeks the sponge became somewhat translucent, took on a tan color, and had a glazed appearance and could not be

separated from the heart except by sharp dissection. After six weeks the gelatin sponge patch was considerably thinned out (See Fig. 4). After eight weeks the sponge was completely absorbed as far as one could determine from the gross appearance. In place of the sponge there was a fibrous plaque which was considerably smaller than the original sponge and which could be separated from the pericardium only by sharp dissection (See Fig. 5). After ten weeks this fibrous plaque became somewhat transparent and the wound in the coronary vessels could be identified as a thin transverse scar. After three months or more this fibrous plaque became so small that it was often difficult to identify the area where the wound in the vessel had been produced.

Evidence of myocardial infarction was observed in only two of the specimens examined. The patency of the coronary artery was determined by arteriography using either an aqueous suspension of red lead or metallic mercury. The former gave better detail in the terminal arterioles, but the mercury gave better contrast of the vessel at the site of the wound. In most of the specimens there was no demonstrable interruption of the opaque medium on roentgen ray, indicating patency of the vessel at the point of injury. Evidence of a constriction or a tortuosity of the vessel at the site of the wound was demonstrated in two dogs. A definite filling defect was observed in three specimens at the level of the wound which indicated obliteration of the vessel for approximately 1 cm. (See Fig. 6 showing arteriograms). In only one of these was there gross evidence of an infarct. The other infarct was found in a specimen where the arteriogram demonstrated a tortuous lumen of the vessel at the site of injury.

Control Series.—In four experiments oxidized gauze was used in an attempt to control hemorrhage from the wounds of the coronary vessels. When two, four, or six layers of the oxidized gauze were used over the bleeding vessel it was found that the bleeding continued through the interstices of the gauze. With eight layers of gauze it was possible to control the hemorrhage as long as finger pressure was maintained on the gauze. However, it was found that the gauze would not adhere to the heart sufficiently well after removal of the pressure of the finger to maintain control of the hemorrhage. Furthermore the oxidized gauze became rather firm after it had been soaked in blood while pressure was being maintained and even if it did adhere to the heart it would not expand and contract with the heart muscle as the gelatin sponge was found to do.

In two experiments the anterior descending branch of the left coronary artery and vein was doubly ligated and transected between the ligatures. Within five minutes there was evidence of cyanosis of the heart muscle distal to the ligature. Within 20 minutes the electrocardiagraphic changes were rather striking. After two weeks a definite infarct of the anterior wall was found. In one animal the entire anterior wall including the apex was involved. This dog died suddenly after eating a hearty meal two weeks after the ligation was done. The other animal which was sacrificed after two weeks had a large infarct of

A

B C

FIG. 6.—Showing arteriograms of specimens (metallic mercury in left coronary).

A. No evidence of constriction, dilatation, or deformity of the vessel where wound was produced 6 months previously (indicated by pointer). Most of the arteriograms were similar to this.

B. Constriction and irregularity of the lumen of the coronary artery where the wound was produced 3 months previously, but no evidence of occlusion of the vessel at this time. One other arteriogram was similar to this.

C. Interruption of opaque medium at point where wound was made 3½ months previously indicating obliteration of the lumen. Two other arteriograms were comparable to this. In one of these there was a gross infarct.

the anterior wall. Although two infarcts were observed in the series in which the vessels were cut with a scalpel, the lesions were not of this magnitude.

Electrocardiography.—Electrocardiograms were taken before, during the course of the operation when the wound of the coronary vessel was produced, or the vessel ligated, and after the operation; the classical limb lead and the

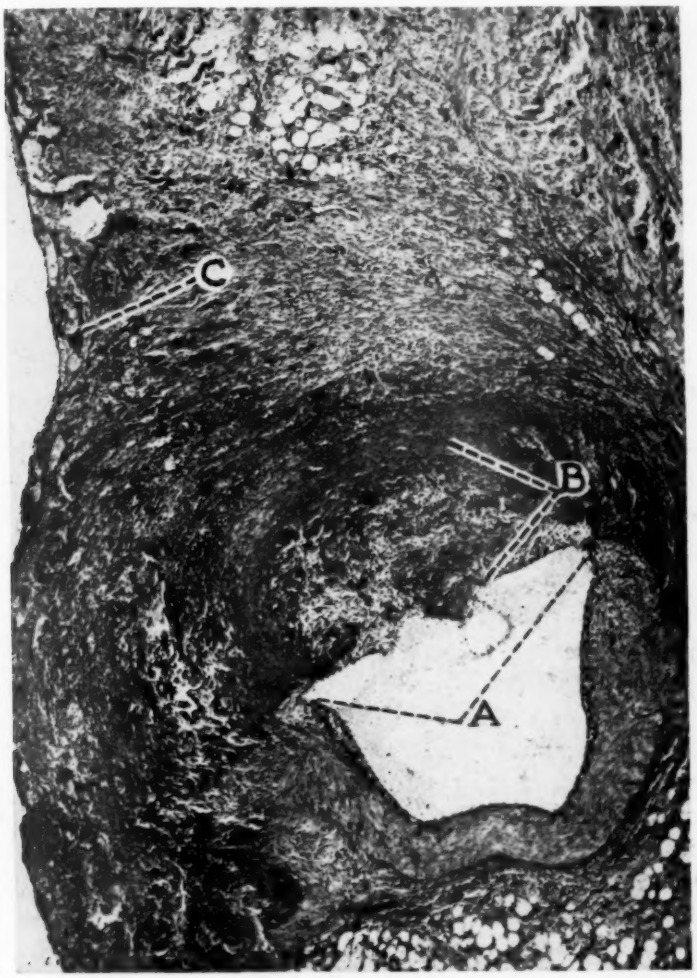

FIG. 7.—Showing photomicrographs of wound of coronary artery after eight days.
A—defect in wall of artery
B—organizing hematoma lined by endothelium
C—fragment of gelatin sponge

chest leads (LI, II, III, CR, CF, CL, and V) were used. The chest lead was static, one interspace below the PMI to avoid the line of incision. Since dog electrocardiograms are exceedingly variable, each dog's preoperative tracing was used as the control for that animal. Generalized normals were not used.

At the time of incision of the coronary vessels Lead III showed a ventricular extrasystole and during the period of bleeding showers of extrasystoles sometimes occurred, followed by the resumption of a normal rhythm and contraction sequence.

In those animals in which there was no gross infarct following incision of the coronary artery, the electrocardiographic changes involved the ST segments and the T waves. There were no significant early changes in the QRS waves. Acutely, and persisting, there was depression of the ST segments and inversion of the T wave; ST changes of similar character were noted in sponge control dogs. Later, T2 and T3 were deformed, becoming diphasic and notched and a Q of significant amplitude appeared in Lead II.

In dogs which had a demonstrable gross infarct after incision of the coronary artery (two experiments) and in the two experiments in which the coronary artery was ligated, the electrocardiograph changes resembled those generally found in infarction of the myocardium, *i.e.*, acute elevation of the ST segment and inversion of the T wave with evolution in subsequent electrocardiograms following the usual pattern of myocardial infarction.

Microscopic Study.—The microscopic study of the coronary vessels was carried out with sections, most of which were cut across the vessel, while some were cut longitudinally. It was necessary to prepare a large number of serial sections to locate the wound in the artery because in many instances it was difficult to determine grossly just where the wound had been produced. One of the most interesting points in this microscopic study was the observation that the wound in the vessel was rather rapidly repaired by endothelialization of newly formed scar tissue (see Fig. 7) under the gelatin sponge patch. In two instances the wound communicated with a small aneurysmal sac which was not previously visualized by the arteriogram. In one instance the serial sections revealed an endothelialized vascular channel through an area of fibroplasia and organizing hematoma which probably represented a small defect between the ends of the transected artery. Later, there was a well formed scar lined by endothelium which sealed off the wound. (See Fig. 8.) In some instances a small outpouching of the lumen could be seen in this scar.

The behavior of the gelatin sponge in the tissues was essentially the same as described previously. There was invasion of the sponge by fibroblasts, deposits of collagen in the sponge, gradual absorption of the sponge by the action of macrophages, and ultimate absorption of the sponge in about two months leaving a small fibrous tissue plaque where the sponge had sealed off the wound in the artery.

COMMENT

The control of hemorrhage from wounds of the coronary artery and vein in experimental animals by a non-suture method—the gelatin sponge "patch"—is of some significance from the standpoint of its possible clinical application where suture would not be feasible and ligation most undesirable. One should not, however, underestimate the technical problem of obtaining hemostasis

under such conditions. It is important to emphasize that a great deal of care and patience is required to obtain satisfactory results with gelatin sponge under such critical conditions. Anyone attempting to use gelatin sponge for hemorrhage of comparable magnitude in patients should spend some time familiarizing himself with the handling of this material under similar experimental conditions

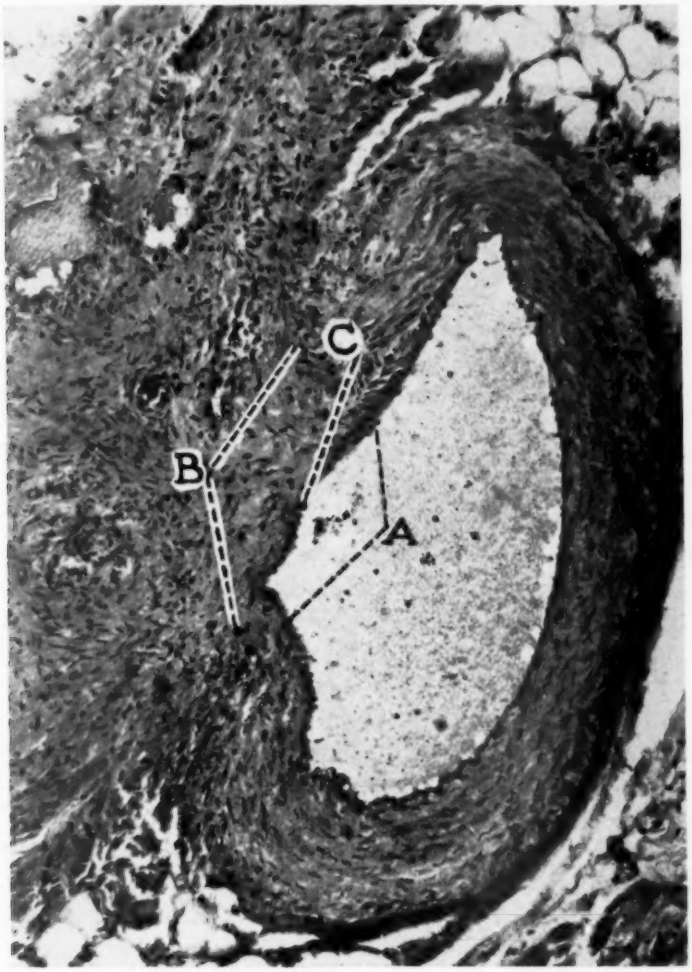

FIG. 8.—Showing photomicrograph of coronary artery where wound was produced three months previously.
A—site of wound
B—replacement of defect in vessel wall by fibrous tissue plaque
C—endothelial lining of fibrous plaque

in animals. It should be stressed that as many as four to five successive sponges were ordinarily used in these experiments and sometimes as many as nine sponges before the massive bleeding was brought under control. Even then an additional reinforcing patch was generally necessary. The fact that it was possible to obtain control of hemorrhage from wounds of the coronary

vessels by this non-suture and non-ligature method and have the animal survive for 48 hours or more in about 70 per cent of the experiments represents a rather critical test of the effectiveness of one of the new hemostatic agents—gelatin sponge.

Of the 11 experiments in which the animal died during, immediately afterwards, or some time during the night after operation, there were four which represent a definite failure of this method, two in which the hemorrhage could not be controlled and two in which there was secondary hemorrhage due to dislodgement of the patch. Of the remaining seven early deaths, most of these could be attributed in varying degree to myocardial ischemia due to cutting of the vessels or to the operative manipulation of the heart. Both of these factors lead to ventricular fibrillation. Of these seven deaths there were four in which the hemorrhage was controlled by the gelatin sponge patch before fibrillation of the heart developed.

When one takes into consideration that interruption of the coronary artery circulation by ligation at the level where the incision was made in most of these experiments has a mortality of 70 per cent,[10] it is not surprising that there is an appreciable mortality to temporary interruption of the circulation such as must occur between the time the wound is produced in the vessels, and the control of the hemorrhage by the gelatin sponge patch. At least 11 per cent of those animals which died promptly after the experiment represent an unquestioned failure of this gelatin sponge patch technic. On the other hand, in 19 per cent of the experiments the early death could be attributed to a considerable extent to the operative procedure on the heart and the wound of the coronary vessels which produced enough disturbance in the cardiac physiology to bring about a lethal outcome.

Another interesting feature of this work aside from the control of hemorrhage by this "patch" method is the rapid healing of the wound in the vessel and the relatively infrequent occlusion of the vessel by thrombosis at the level of the wound. In only three specimens did the arteriogram demonstrate a complete occlusion. These were in animals which survived one week, three months and three and one-half months respectively. In one of these there was a definite infarcted area but it was smaller than that observed after ligation at this level. In two of the arteriograms there was some evidence of constriction or deformity of the vessel at the level of the wound. In one of these there was an infarction of the myocardium. It is presumed that the patency of the vessel by arteriography may represent a recanulization of the vessel after occlusion by thrombosis, which originated at the level of the wound. The relatively good healing of the wound in the vessels which were "patched" with gelatin sponge is apparently due to the rapid endothelialization of the vascular channel between the edges of the wound under the protective cover of the gelatin sponge patch.

The electrocardiographic studies in these experiments were of interest primarily from the standpoint that the characteristic changes generally seen

after coronary occlusion, and found in the ligature control series, did not occur after cutting the vessel and restoring the blood flow with the aid of the gelatin sponge patch. Such changes as did occur in the electrocardiogram following transection of the vessel resembled "strain patterns," characterized by inversion of TI, depression of ST segments, and changes in the contours of the T waves, except for the two instances where infarction occurred and in these tracings the changes were comparable to those found after ligation.

It is recognized that the interpretation of the electrocardiograms in dogs represents somewhat of a problem and a more detailed report of this phase of the work will be made subsequently. It is believed that the method of taking electrocardiograms which can be read and identified while the experiment is in progress represents a distinct advantage in work of this type. As a result of the stimulus from this experimental work, it is planned to install a visual recording electrocardiograph in the hospital operating rooms for tracings on patients especially of the older age group so that a better evaluation of the cardiac status can be obtained during the course of prolonged anesthesia for radical surgery.

The failure to obtain control of hemorrhage from wounds of the coronary vessels with oxidized cellulose is of some importance in evaluating the properties of this hemostatic agent. The use of oxidized cellulose for wounds of the *vena cava* in dogs was also found to be unsatisfactory. The principal point which was observed was that the oxidized cellulose would control the hemorrhage as long as finger pressure was maintained and if rather thick pads were used. However, there was relatively little tendency for the oxidized cellulose to adhere to the heart or the *vena cava* after the finger pressure was removed, and thus the control of hemorrhage was not maintained. This brings up the basic difference in these two hemostatic agents: the oxidized cellulose appears to act primarily as a chemical coagulating agent, whereas the gelatin sponge acts as the structural support for a blood clot. Thus, one could say that the principal indication for the use of gelatin sponge is where the control of hemorrhage can best be accomplished and maintained by a "reinforced clot." These observations do not in any way negate the value of oxidized cellulose for many of the problems of hemostasis in surgery where an absorbable coagulating medium is indicated, but rather suggest that in some types of hemorrhage the gelatin sponge may be more effective.

In these experiments on dogs, no thrombin was used in the gelatin sponge. Thrombin was omitted primarily to evaluate the effectiveness of the sponge alone. Furthermore, the thrombin may be definitely contraindicated where the gelatin sponge is used for control of hemorrhage from blood vessels as it could probably contribute to intravascular thrombosis if any of the thrombin escaped into the lumen of the vessel.

SUMMARY

In a series of 37 experiments on dogs, a scalpel wound was produced in the anterior descending branch of the left coronary artery and vein. The hemor-

rhage was controlled by the application of a gelatin sponge patch and the animal survived the immediate operative period in 70 per cent of the experiments. In 11 per cent of the experiments, this "patch" technic was a failure. In 19 per cent of the experiments the animal died from the effects of temporary interruption of the coronary circulation, manipulation of the heart or the anesthesia.

CONCLUSIONS

The gelatin sponge patch technic may provide a desirable means of controlling hemorrhage from wounds of coronary vessels and thus restoring blood flow in a vital vessel where suture may not be at all feasible and ligature not desirable. For wounds of the coronary vein alone, the "patch" technic is relatively simple; however, for wounds involving the coronary artery it is doubtful that one could expect satisfactory results in patients without previous experience with this technic in experimental animals.

The control of hemorrhage by gelatin sponge under the conditions obtaining in this experimental study represents a rather critical test of the effectiveness of this hemostatic agent.

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TOTAL GASTRECTOMY FOR CARCINOMA OF THE STOMACH*

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THE FIRST COMPLETE RESECTION of the stomach in man was performed by Phineus Conner of Cincinnati, in 1884.[1] The patient, moribund at the time of operation, died on the table and it was not until 1897, 13 years later, that Schlaetter of Zurich was able to report the first successful total gastrectomy.[2] This patient lived for 14 months before dying of a recurrence of the carcinoma. In 1898, four American surgeons, Brigham,[3] MacDonald,[4] Richardson,[5] and Harvie,[6] each successfully removed the entire stomach from patients suffering from gastric carcinoma. The patients of Brigham and MacDonald were reported to be alive and well eight and seven years respectively, after operation.[7]

In 1928, 31 years after the first successful total gastrectomy, Finney and Rienhoff[8] reviewed the literature and found reports of 67 total gastrectomies for carcinoma. The operative mortality was 53.8 per cent. In a similar group of 55 patients subjected to radical gastrectomy, but with the preservation of 3 c. or less of gastric wall at either the esophageal or duodenal end, there was an operative mortality of only 25 per cent. Finney and Rienhoff concluded that, "a more beneficial result clinically, physiologically, and mechanically is to be expected if one leaves a portion, ever so small, of the gastric mucosa."

By 1942 the reported number of total gastrectomies for carcinoma had risen to 298 and the operative mortality had dropped to 37.6 per cent.[9] Of the 186 patients surviving operation only 16 or 8.5 per cent were known to have survived for more than three years. Metastatic or recurrent carcinoma was believed to be the cause of death in 82.5 per cent of the patients who survived operation but later died.

In more recent reports[10, 11, 12, 13] the operative mortality has varied between 10 and 30 per cent, Table I, and although about half of the patients who survive operation die within a year or 18 months, approximately 20 per cent can expect to live for three years or longer.[10]

Studies of the nutritional status of patients who have survived total extirpation of the stomach have resulted in conflicting reports. Farris[14] and associates, after studying a group of patients at the University of Michigan, stated that the stomach does not play an essential role in the digestion of fats and proteins. It was also their conclusion that while gastrectomy interferes with the metabolism of iron, primary anemias are rarely encountered. In the

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same year, 1943, Rekers[15] and associates in reporting the results of studies made at the Memorial Hospital, in New York, stated that "patients who have had total gastrectomy for carcinoma of the stomach have an impaired ability either to digest or absorb the fat of the diet and, in one patient, the protein of the diet." In these same patients they observed "a refractory rather than a macrocytic anemia." MacDonald[7] and associates, in 1947, reported studies on three patients who had survived total gastrectomy for three, five, and ten years, respectively. The three and ten year survivors were said to be in excellent condition. Their fat absorption was not significantly impaired. The

TABLE I.—*Total Gastrectomy*

Authors	Year of Report	Number Operations	Mortality
Finney and Reinhoff[9]	1928*	67	55.8%
Pack and McNeer[9]	1942*	298	37.6%
Waugh and Fahland[16]	1945	77	44.2%
Smith[10]	1947	89	29.1%
Ransom[12]	1947	60	23.0%
Pack, McNeer, Boohn[11]	1947	41	31.7%
Longmire[13]	1947	20	10.0%
Smithwick[17]	1947	10	20 0%

* Review of literature.

TABLE II.—*Gastrectomy Esophagojejunostomy*

Years	Number Operations	Number Deaths	Mortality
1938–1944	7	5	71%
1945–1948	11	2	18%
Total	18	7	39%

third patient, a five year survivor, who had a partial pancreatectomy in addition to total gastrectomy, showed impairment of fat absorption. Two of the three patients developed a macrocytic hyperchromic anemia, two and five years after operation. The third patient had prophylactic liver therapy and did not develop anemia.

There is little information available concerning those patients who survive operation and later die from inanition. Longmire[13] reported two such patients among ten postoperative deaths. Since both patients had been discharged from the hospital and apparently were receiving inadequate diets he concluded that these patients would have survived if they had been provided with ordinary dietary requirements. In reporting 43 late deaths following total gastrectomy Smith[10] stated that seven, or 16 per cent, died from inanition. The details of these deaths are not recorded.

Our observations lead us to believe that some deaths reported as due to metastases or a recurrence of the carcinoma actually may have been caused by inanition.

CASE MATERIAL

Our experience in treating carcinoma of the stomach by gastrectomy with esophago-jejunostomy is limited to 18 cases. There were seven deaths, an operative mortality of 39 per cent. There have been only two fatalities among the 11 patients operated upon since 1944, an operative mortality of 18 per cent (Table II). The causes of death are shown in Table III. Three patients died from infection, presumably caused by a leak of the esophago-jejunal anastomosis, two died of shock, one developed a fatal pneumonia and one death was caused by a pulmonary embolus.

TABLE III.—*Causes of Operative Deaths*

Name	Year	Survival Period	Cause of Death
A. V.	1940	3 Months	Peritonitis
T. S.	1940	1 Day	Shock
T. E.	1944	1 Day	Shock
H. O.	1944	6 Weeks	Peritonitis
K. H.	1944	15 Days	Pulmonary embolus
J. F.	1945	11 Days	Peritonitis
M. N.	1945	6 Days	Pneumonia

TABLE IV.—*Causes of Late Deaths*

Name	Survival Period	Cause of Death
E. H.	4 Years	Metastases
F. D.	1 Year	Recurrence
B. G.	7 Months	Recurrence
P. Q.	10 Months	Recurrence
C. G.	6 Months	Recurrence
W. B.	7 Months	Inanition

Six of the 11 patients surviving operation are now dead. The survival period and the causes of death are shown in Table IV. One patient lived for four years before dying from metastases. The remaining five patients lived one year or less; four died because of a local recurrence of the carcinoma and one patient died from inanition although he had an excellent appetite and spent most of his postoperative life in the hospital where every effort was made to improve his nutritional state.

The present condition of the five patients who are alive is shown in Table V. Although it cannot be said that any of these people have been returned to a completely normal physical state, they are living fairly comfortable lives, one for 30 months, one for 22 months, two for three months and one for one month.

The present study is concerned primarily with the subsequent history of patients who have survived gastrectomy. We are reporting in some detail our observations on three patients. One lived for four years before dying from metastases, the second died from inanition seven months after operation, and the third is alive and fairly well, 30 months after operation.

The first patient (E. H.) was operated upon in December, 1938, and the entire stomach was removed. She died in November 1942. Death was thought to be caused by metastatic carcinoma; this diagnosis being based on roentgen evidence of tumor in the pelvic bones, the presence of an enlarged liver and ascites. Post mortem examination was not done as the patient died in another hospital.

While this patient was never robust following operation and did not return to any gainful occupation, she led a reasonably comfortable life for more than

TABLE V.—*Present Condition of Survivors*

Name	Postoperative Interval	Weight	Appetite	Food Capacity	Stools	Blood	Work
A. B.	30 Months	Loss 34 lbs.	Poor	3 meals a day. Occasional vomiting.	Normal, 1 per day. No diarrhea.	RBC 4.3 Hb 98% Serum protein 7.3	Light housework
M. L.	22 Months	Loss 10 lbs.	Poor	Frequent feedings	2-3 per day. Occasional diarrhea.	RBC 4.0 Hb 80%	Regular Secretary
W. M.	3 Months	Loss 10 lbs.	Good	Frequent feedings	Normal, 1 or 2 per day. No diarrhea.	RBC 3.6 Hb 70%	None
J. R.	3 Months	Gain 10 lbs.	Good	Frequent feedings	Normal, 2 per day. No diarrhea.	RBC 4.1 Hb 75%	None
A. W.	1 Month	Loss 2 lbs.	Fair	Frequent feedings	Normal, 1 or 2 per day. No diarrhea.	RBC 4.0 Hb 80%	None

three years before developing symptoms which presumably were due to metastases. Blood counts made at frequent intervals revealed an anemia, characterized by a hemoglobin of between 60 and 70 per cent and a red cell count of about 3,500,000, which persisted in spite of almost continuous iron (ferrous sulfate) and liver therapy. Coincident with the roentgen findings of bone metastases, three and a half years after operation, a marked increase in the degree of anemia was noted. It is the opinion of Dr. Luis A. Amill, who followed this patient in the hematology clinic, that at no time was the anemia of the primary type.

Although edentulous, this woman ate fairly well on her several admissions to the hospital, but due to her low economic status it is probable that her food intake at home was not ideal. Even so, she maintained a weight of between 90 and 100 pounds. Her normal weight had been about 110 pounds. She did not

at any time suffer from a disabling diarrhea and ordinarily had two or three bowel movements a day. Examination of the stool one year after operation showed a fat content of 49 per cent and at one year and nine months the fat content was 34 per cent.

A deficiency of protein digestion was suggested by persistently low total serum protein levels and the fact that it was repeatedly noted on the patient's chart that she had a mild nutritional edema.

The second patient (W. B.) was operated upon in July, 1947, and the entire stomach, except 3 cm. of the pylorus was removed. He died of inanition in February, 1948. His course was uncomplicated until the eleventh postoperative day, when he developed diarrhea. This diarrhea persisted, with the exception of short periods of three or four days, until the patient's death seven months later. Intensive medical and dietary treatment failed appreciably to alter the number or character of the stools. The fat content of the stool determined on one occasion, six months after operation, was found to be 40 per cent.

This patient's normal weight was about 140 pounds although at the time of admission to the hospital he weighed only 120 pounds. Following operation his appetite was ravenous and after about two weeks he regularly consumed six feedings per day of a high protein, high caloric and high vitamin diet. His weight, on discharge from the hospital, five weeks after operation was 117 pounds.

He did not do well at home and was readmitted to the hospital, three weeks after discharge, complaining of a persistence of the diarrhea and a weight loss of 19 pounds. This patient spent the remainder of his life, about five months, in the hospital where strenuous efforts in the way of oral and parenteral feedings were made to improve his nutritional status.

In spite of the high protein diet, supplemented by oral and intravenous protein hydrolysates, serum protein values dropped from an immediate postoperative level of 7.4 Gm. per cent to less than 6 Gm. per cent, and remained below this level. A mild though progressive dependent edema was present. During the last month of life the edema was quite marked and ascites developed.

A mild degree of anemia, as indicated by an average hemoglobin value of 75 per cent and a red cell count of about 4,000,000 persisted in spite of ferrous sulfate therapy. Liver was not given to this patient.

Post mortem examination showed extreme emaciation. There was practically no subcutaneous fat and the omentum as well as the mesentery of the intestines was devoid of fat. There was no evidence of carcinoma, local or metastatic. Consolidation of the right lower lobe of the lung was present but this was regarded as a terminal development. The primary cause of death appeared to be starvation, due to an inability to digest or absorb adequate food from the intestinal tract.

We had no satisfactory explanation as to why this patient was unable to digest enough food to sustain life. One possible factor is that in 1937, 10 years before the gastrectomy, the patient's right colon had been removed because of a carcinoma of the hepatic flexure. However, excellent health for

nine years following the partial colectomy suggests that this operation had little to do with his failure to maintain a satisfactory nutritional state following gastrectomy.

The third patient (A. B.), a 59-year-old woman, was operated upon in October, 1945, and the entire stomach, except approximately 4 cm. of the pylorus, was removed. In April, 1948, 30 months later, she was in fairly good health, able to do her own shopping, and a large part of her usual housework. The most striking feature of this patient's course has been a total weight loss of 34 pounds, 6 pounds of it in the past year. She has not had a particularly good appetite, but does eat three small meals a day and further supplements her food intake by candy between meals. The chronic constipation complained of prior to operation disappeared and the patient has had one large but normal bowel movement each day. Medication has been limited to an iron compound and multiple vitamin tablets. At the last examination, 30 months after operation, the blood count was 4,300,000 red blood cells with a hemoglobin of 98 per cent and the total serum protein was 7.3 per cent.

COMMENT

As previously indicated, two cases included in this report are not true total gastrectomies. In one (W. B.) 3 cm. of the pylorus was not removed and in the second (A. B.) approximately 4 cm. of the pylorus was left. The small amount of gastric mucosa was spared in the hope that its presence might reduce the nutritional difficulties which are known to occur in some patients subjected to total gastrectomy.

The preservation of gastric mucosa in the patient (W. B.) had no apparent beneficial influence on his most unsatisfactory course. The outcome in the second patient (A. B.) with approximately 4 cm. of pylorus, has been satisfactory except for a marked weight loss.

Our experience with two other patients, not included in this series, strengthens the impression that even small amounts of gastric mucosa may be of benefit to the patient. The first of these patients (H. M.) had an almost complete gastrectomy for the removal of a neurofibroma of the fundus, only 6 cm. of the cardia being left. This man, after a long convalescence during which the "dumping syndrome" made his life most uncomfortable, returned to work as an automobile mechanic. On the last examination, 22 months after operation, he was gaining weight and weighed 132 pounds. Normal preoperative weight was 156 pounds. He had a fairly good appetite and regularly ate six small meals a day. Bowel movements were normal and there was no anemia.

The second patient (J. U.) was operated upon for the removal of a gastric carcinoma. All the stomach, except 6 cm. of normal appearing pylorus, was excised and the esophagus was anastomosed to the remanant of pylorus. Convalescence was prolonged due to stricture at the site of anastomosis but at the last examination, 12 months after operation, this man appeared to be in good health. He had a fairly good appetite although a limited food capacity forced him to eat frequent small meals. His weight was 105 pounds, a gain of about

nine pounds since discharge from the hospital. Preoperative weight had been 116 pounds. Examination of the blood revealed a hemoglobin of 94 per cent, 4,700,000 red blood cells and a total serum protein of 7.4 Gm. per cent.

No definite conclusions can be drawn from the small number of cases herein reviewed, but three of the four patients in whom a small amount of stomach was retained appear to have enjoyed a better nutritional state than those in whom the entire stomach was removed. This observation is in accord with that of Finney and Rienhoff[8] and suggests that further observations are needed on this and other points connected with total gastrectomy. It is disturbing to have a patient survive total gastrectomy only to die later of inanition after apparently being cured of his carcinoma.

SUMMARY

1. Eighteen patients with carcinoma of the stomach were treated by total gastrectomy. There were seven deaths, an operative mortality of 39 per cent.

2. Six of the 11 survivors are now dead. One patient lived for four years, one for one year and four died within one year following operation.

3. Five of the six deaths were due to a recurrence of the carcinoma. One patient died of inanition seven months after operation although his food intake had been adequate. Post mortem examination revealed no evidence of carcinoma.

4. Five patients were alive at the time of this report. One for 30 months, one for 22 months, two for three months and one for one month.

5. The four patients followed from one to four years have maintained a fairly satisfactory, though subnormal nutritional state.

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CHEMOSURGICAL TREATMENT OF TUMORS OF THE PAROTID GLAND*†

A MICROSCOPICALLY CONTROLLED METHOD OF EXCISION

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IN THE TREATMENT OF TUMORS of the parotid gland the main object is the complete removal of the neoplasm. A second object is the preservation of as much as possible of the facial nerve which traverses the parotid gland. The attainment of these goals is facilitated by the use of the chemosurgical technic which, by virtue of its microscopic control of excision, enables the eradication of neoplasms with an unusually high degree of reliability and with maximal conservatism. The development of the chemosurgical method in the laboratory[1] and in the clinic,[2] and its application in the treatment of cancer of the lip,[3] nose,[4] ear,[5] eyelid,[6] face,[7] extremities and trunk[8] and skin[9] have been described.

TECHNIC

The chemosurgical technic as applied to the excision of tumors of the parotid gland will be described in the case report which follows:

Case Report.—W. H., male, age 80, was admitted to the Wisconsin General Hospital complaining of a growth under the left ear. The lesion which began as a deep-seated mass in the parotid gland was first noticed by the patient about 6 months previously. The mass had grown rapidly despite radium and roentgen ray therapy. One month before admission a lobule in the posterior portion of the mass had rapidly broken through to the surface of the skin and an ulcer had developed at its apex.

Just below the ear and impinging upon it was a deep-seated mass which measured 6.5 by 8.0 cm. (Fig. 1A). Near the posterior edge there was a protrusion which measured 3.5 by 4.5 cm., and in the center of this was an ulcer which measured 1.7 by 1.9 cm. The mass pressed up against the ear and external auditory canal with resulting deformity of these structures. The neoplasm was firmly fixed to the parotid gland and other deeper structures. There was no facial paralysis.

Following premedication with 0.015 Gm. of morphine sulfate the first step in the treatment of this lesion was the application of a keratolytic, dichloracetic acid, to the portion of the mass covered by skin. Whitening of the skin served to indicate when the keratin layer had been penetrated and rendered permeable to the zinc chloride. The zinc chloride fixative paste was then applied in a thickness of about 3 mm. The paste contained stibnite (80 mesh sieve), 40 Gm.; powdered sanguinaria, 10 Gm.; and saturated solution of zinc chloride, 34.5 cc. The treated area was covered with a thin layer of cotton and then by a layer of cotton on which petrolatum had been spread to make a moisture-tight closure.

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After 24 hours a layer of tissue about 1 cm. thick was excised. There was no pain or bleeding from this operation because the incision was made through killed and fixed tissue. The presence of neoplasm was evident upon gross inspection. Frozen sections of the fixed tissue revealed the presence of a squamous cell carcinoma with a degree of malignancy of grade 3 (Fig. 4A). The fixative was reapplied.

During the next four days the tumor mass was removed in successive layers without microscopic examination of the excised tissues. On the fifth day, however, it became impossible to differentiate grossly between normal and cancerous tissues in some areas.

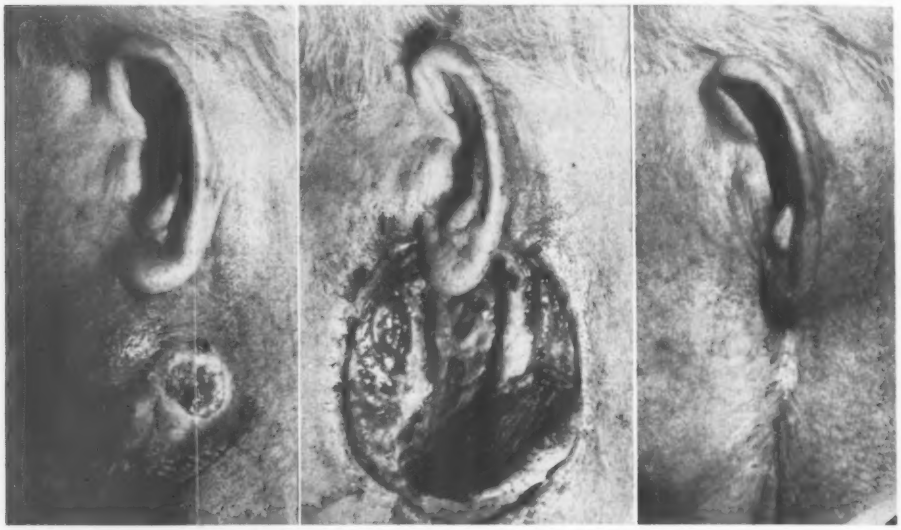

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FIG. 1.—(A) Parotid carcinoma which had grown rapidly over a period of six months and had failed to respond to x-ray and radium treatment. The main mass was deep-seated but there was an ulcerated protrusion of one month's duration from the posterior part of the neoplasm. (B) Lesion after separation of the final layer of fixed tissue except for a portion over the sternocleidomastoid muscle near the lower edge. Deep extensions from the main mass which followed along the perimesium of the stylohyoid muscle and along the perineural lymphatics of the auriculotemporal nerve were removed by multiple microscopically controlled excisions. (C) Healed lesion two months later. There was no facial paralysis except for the muscles of the chin supplied by the mandibular branch. The patient was free of cancer after seven years.

Therefore, the layers of tissue from the areas in question were divided into specimens of convenient size; frozen sections were cut through the under surface of each by means of microtechnical procedures which have been described.[10] The sections were scanned under the microscope and the areas of cancer so found were marked with red pencil on a map drawn on a pad of paper. This map corresponded to a map drawn on the lesion with merbromin during the excision of the specimens. Reapplication of the fixative was then limited to the areas demonstrated to be cancerous by microscopic visualization.

This process was repeated daily until the 20th day when the removal of the last extension of the cancer was completed. In some areas the microscopically visualized extensions of the neoplasm extended more than 2 cm. beyond the grossly visible portion. One extension followed the perineural lymphatics of the auriculo-temporal nerve for several millimeters while another followed the perimesium of the stylohyoid muscle. Without the systematic microscopic control afforded by the chemosurgical method these extensions undoubtedly would have been missed.

It is important to emphasize that the technic made it feasible to examine every square millimeter of the lesion under the microscope and to proceed till the entire area was free of cancer.

Five days after reaching a cancer-free plane the thin final layer of fixed tissue had become demarcated so that most of it could be dissected off (Fig. 1B). Upon return for checkup two months later the lesion had completely healed with a fine linear scar (Fig. 1C). The patient was free of cancer when last seen seven years later. Despite the extensiveness of the lesion there was no facial nerve paralysis except for the unimportant mandibular branch.

In the absence of palpable regional nodes and in consideration of the advanced age of the patient a neck dissection was not done. In a younger patient with a carcinoma of such large size and high malignancy, a prophylactic

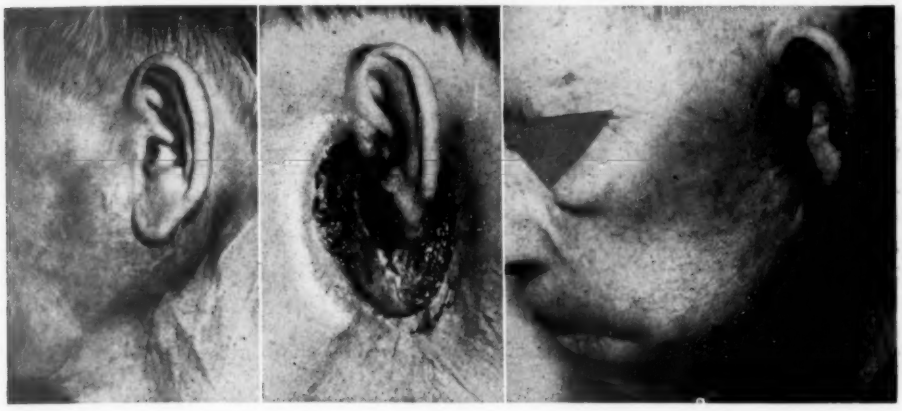

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FIG. 2.—(A) Carcinoma of the parotid gland. One year prior to admission, a mass which had been diagnosed "mixed tumor of the parotid" was surgically excised and the area treated with x-ray. The recurrent mass was hard and fixed and it measured 60 by 63 mm. (B) Lesion after chemosurgical excision. Because of the definitely infiltrative character of the neoplasm (Fig. 4B) a diagnosis of carcinoma was made. The neoplasm infiltrated around the main branches of the facial nerve so complete paralysis resulted from the chemosurgical removal. The inferior wall of the external auditory canal was also invaded. (C) Healed lesion three months later. The complete facial paralysis is apparent. There has been no recurrence after three years.

neck dissection would have been recommended. Palpable enlargement of the nodes also would have called for neck dissection. It may be advisable in some cases to do both a carotid ligation and a lymphadenectomy during or prior to chemosurgical excision of the primary lesion. Such a procedure not only would accomplish the removal of the nodes suspected of containing cancer but it would also avoid the danger of hemorrhage during the chemosurgical treatment of the parotid lesion.

In some cases in which deep invasion into the region of the external carotid artery is foreseen the ligation of this vessel just above the carotid bifurcation is advisable in order to prevent hemorrhage during separation of the final layer of fixed tissue. There were four instances of bleeding sufficient to require

a suture-ligature or a pressure dressing in the 17 cases in this series. This complication could have been avoided by ligation of the external carotid, either before institution of chemosurgical treatment or after the sections had revealed that there were deep extensions of cancer along this vessel. No instance of serious hemorrhage occurred in the patients whose cases are reported in this series.

In two patients whose cases are reported in this series the external carotid artery was ligated. One ligation was done prior to the institution of chemosurgical treatment because the carcinoma obviously had extended very deeply. The other ligation was carried out because it was determined, during chemosurgical treatment, that the carcinoma had extended around this vessel.

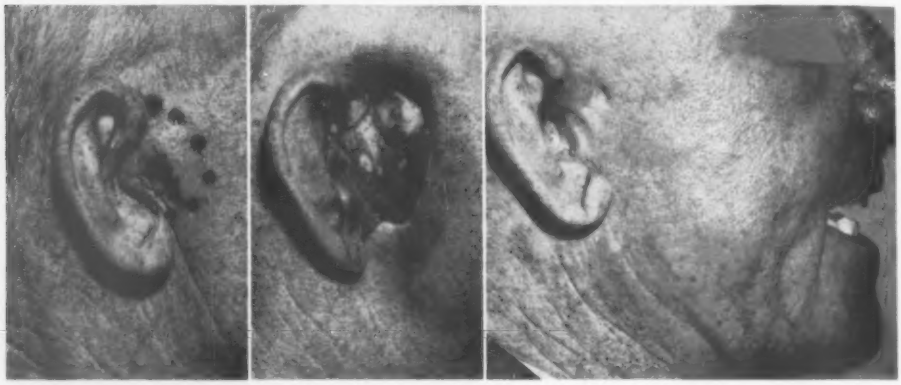

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FIG. 3.—(A) Carcinoma of the parotid of two years' duration. A tumor had been excised in another department and the area treated with radium one year before he was admitted to the chemosurgical department. (B) Lesion after chemosurgical excision in nine microscopically controlled stages and after separation of the final layer of fixed tissue. The carcinoma (Fig. 4C) extended onto the bone of the external auditory canal, the temporal bone, the zygoma and the condyloid process of the mandible which structures are shown in the base of the wound. Some areas of mixed tumor were found indicating that the carcinoma arose in a pre-existing mixed tumor. The carcinoma invaded for several millimeters along the perineural lymphatics of the branch of the facial nerve (Fig. 4D) to the frontalis muscle which was paralyzed. (C) Healed lesion with partial closure of the auditory canal. The lack of lower facial paralysis is evident. There was some weakness of the lower eyelid so that a tarsorrhaphy was done although this probably was unnecessary. The patient is free of cancer after four years.

Some neoplasms of the parotid gland retain considerable secretory function and the lesion may be so moist that penetration of the fixative chemical is reduced due to dilution. In several cases it was necessary to reapply the fixative twice instead of once daily.

Salivary fistulas which persisted for periods of from one week to 21 months were encountered in 15 of the 17 patients whose cases are reported in this series. In only four cases did the fistula persist longer than three months. During the healing of lesions of the parotid gland after chemosurgical treatment, part of the surface is covered by epithelium derived from the parotid ducts. Ordinarily, this parotid epithelium is gradually replaced by the

epithelium of the skin, the latter apparently being more able to survive the conditions on the surface of the body. However, if complete replacement by the skin epithelium does not occur promptly, the fistula may be eradicated by the simple expedient of applying the zinc chloride fixative to the exposed

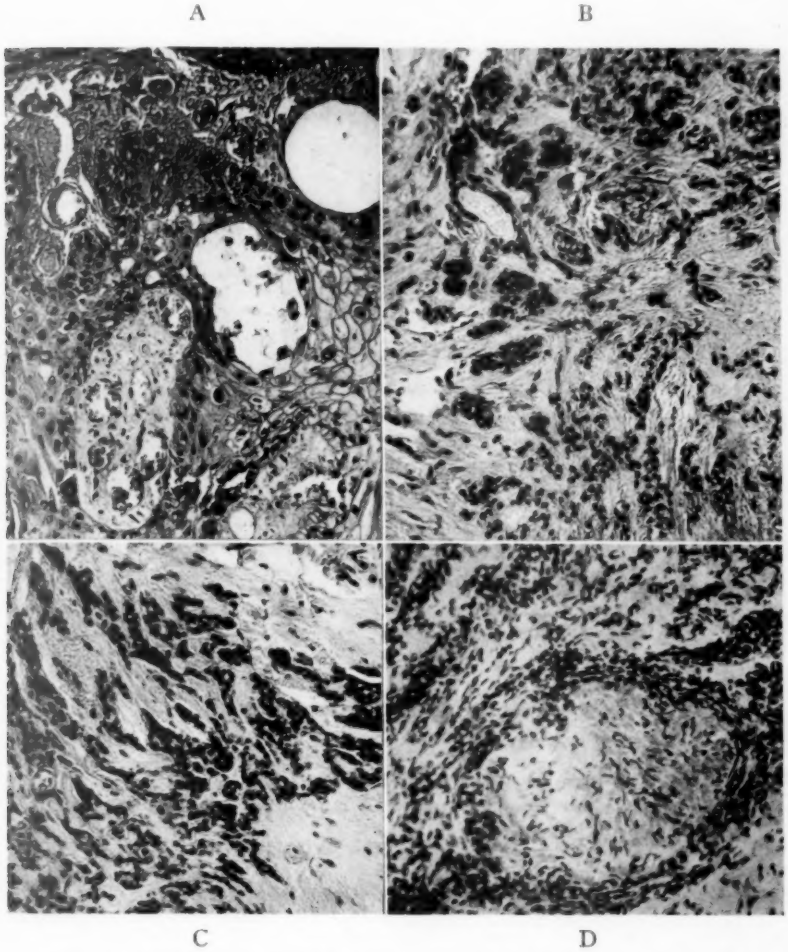

FIG. 4.—Sections of parotid carcinomas after fixation *in situ* by zinc chloride. (A) Squamous cell carcinoma from patient shown in Fig. 1. The large clear cells were degenerated rather than keratinized. The degree of malignancy was considered grade 3. (B) Carcinoma from patient shown in Fig. 2. A moderate degree of invasiveness is evident. (C) Carcinoma from patient shown in Fig. 3. This moderately invasive neoplasm arose in a pre-existing mixed tumor. (D) Same tumor, showing perineural invasion.

parotid epithelium. In every case in this series in which troublesome parotid fistulas were encountered, this method was effective in eliminating the condition. Even an apparently permanent fistula of 21 months' duration was healed in ten days after institution of this treatment.

THERAPEUTIC RESULTS IN CASES OF CARCINOMA OF THE PAROTID GLAND

Thirteen carcinomas of the parotid gland were chemosurgically treated during the seven-year period ending November 30, 1944, which date is over three years prior to this writing. Most of the lesions were large and deep-seated. Nearly two-thirds of the patients (63.6 per cent) had received previous unsuccessful surgical excision or radiation treatment. In none of the cases was the presence of metastasis recognized at the onset of treatment.

End Results After Three Years or More.—The 13 cases observed for three years or more were divided into "indeterminate" and "determinate" groups according to the plan of Martin, MacComb and Blady.[11] The indeterminate

TABLE I.—*End Results of Chemosurgical Removal of Carcinoma of the Parotid Gland*

This series includes the cases of all patients with histologically proven carcinomas both early and advanced, previously untreated and recurrent, who were admitted to the chemosurgery clinic from March 26, 1938 to November 30, 1944 for the three year group, and from March 26, 1938 to May 1, 1943 for the five-year group.

	Three-Year Period	Five-Year Period
Total number of cases	13	12
Indeterminate group		
Patients without recurrence, dead from other causes	1	1
Patients without recurrence, lost from observation	1	1
Total number	2	2
Determinate group		
Total number	11	10
Unsuccessful results		
Patients dead as a result of cancer	4	4
Patients with cancer lost from observation	0	0
Patients with cancer living	0	0
Total number	4	4
Successful results		
Patients free from cancer for three years or more	7	
Patients free from cancer for five years or more		6
Three-year end results		
Total number of cases with successful results divided by total number of determinate cases (7 ÷ 11)	63.6%	
Five-year end results		
Total number of cases with successful results divided by total number of determinate cases (6 ÷ 10)		60%

group included one patient who died of other causes before the expiration of three years without recurrence of the cancer and one patient who was lost from observation without evidence of cancer when last seen. The determinate group included the unsuccessful results of which there were 4 and the successful results of which there were 7. Thus, in the three-year period successful results were obtained in 63.6 per cent of the 11 cases in the determinate group (Table I).

End Results After Five Years or More.—In the group of 12 cases observed for five years or more, there were two cases in the indeterminate group and ten cases in the determinate group. In the five-year period, successful results were obtained in 60 per cent of the ten cases of the determinate group (Table

I). In one case which was illustrated in a previous article[2] the patient has remained free of cancer for eleven years.

Effect of Size of Lesion on Prognosis.—As was to be expected the rate of cure was greater for the smaller lesions than for the large (Table II). Thus, while 100 per cent of the lesions under 4 cm. in diameter were cured, only 50 per cent of the lesions over 4 cm. in diameter were cured. However, it is not the lesion's extensiveness *per se* that reduces the curability of parotid carcinomas, but it is the increased chance of metastasis or involvement of vital structures that impairs the prognosis of patients with lesions of large size. Thus, in this series in which there were four unsuccessfully treated patients there were two failures due to the development of metastases, one failure due to extremely extensive permeation along the perineural lymphatics and one operative death resulting from pulmonary edema and bronchopneumonia in a patient who was in very poor condition when therapy of the extremely advanced parotid tumor was instituted. Therefore, if there has been no complication such as metastasis or involvement of vital structures, it is possible chemosurgically to excise even the most extensive tumor.

TABLE II.—*Effect of Size of Carcinoma of Parotid Gland on Prognosis*

Group	Average Diameter (cm.)	Number of Lesions	Successful Results	
			Number	Per Cent
A	Under 2	0	..	...
B	2 to 4	3	3	100
C	4 to 6	4	2	50
D	6 or more	4	2	50
All groups	.....	11	7	63.6

Effect of Previous Treatment on Prognosis. In the group of eleven cases of carcinoma of the parotid gland in the determinate group, seven lesions (63.6 per cent) had recurred after previous unsuccessful surgical excision or radiation therapy. Although it would be expected that previous treatment would have an unfavorable influence upon prognosis, the opposite seemed to be true in this series of cases. Thus, in the seven cases in which the patient had recurrent carcinoma, the neoplasm was successfully treated with the chemosurgical technic in five (71.4 per cent) while in the four cases of patients with lesions which had not received previous treatment, successful results were obtained in only two (50 per cent). While too much significance should not be attached to the statistics in this small series of cases, it is evident that the chemosurgical method is particularly useful in the treatment of recurrent lesions because these would otherwise carry a very poor prognosis. The only adverse influence previous unsuccessful treatment has upon the prognosis as far as chemosurgical treatment is concerned is occasioned by the delay which allows metastasis and invasion of vital structures to occur.

Effect of Histologic Grade of Malignancy on Prognosis.—Although there is no generally accepted classification of carcinoma of the parotid gland into

well defined grades of malignancy, a definite impression was gained that prognosis is strongly affected by the histologic degree of malignancy. Thus, in a group which we have classified as "moderately invasive carcinoma" (*e.g.*, Fig. 4B) all four cases were successfully treated while in another group of four cases placed under the classification "highly invasive carcinoma" the rate of cure in the three-year period was only 50 per cent. The latter group includes the one squamous cell carcinoma in this series (Fig. 4A). The remaining three cases were placed under the classification "moderately invasive carcinoma arising from a mixed tumor (*e.g.*, Fig. 4C & D) and in this group the rate of cure was 33.3 per cent." The unsuccessful treatment of two cases in this group is readily accounted for on the basis of the extremely extensive nature of the neoplasms rather than on their degree of malignancy. The two unsuccessfully

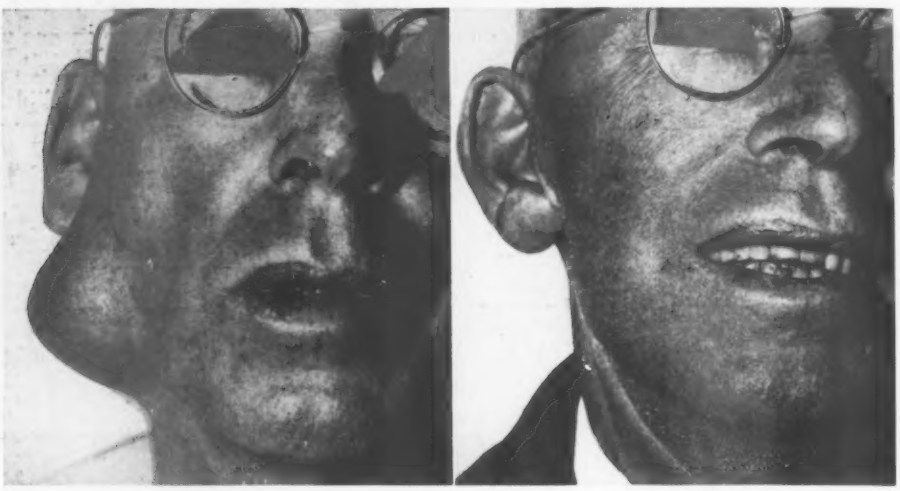

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FIG. 5.—(A) Benign mixed tumor of the parotid gland of eight years' duration. (B) Healed lesion. The lack of paralysis is evident. There has been no recurrence of the tumor after nine years.

treated cases in the group of highly invasive carcinomas had unfortunate outcomes because of metastasis in one and because of widespread invasion of the perineural lymphatics in the other. The successfully treated case in this group was a deep-seated carcinoma with cervical metastasis; the patient was well five years after chemosurgical removal of the primary lesion followed by surgical dissection of the cervical nodes.

Effect of Site of Origin on Prognosis.—The site of origin of the carcinoma had relatively little effect on the prognosis. Thus in the eight cases arising in the retromandibular area, five were successfully treated (62.5 per cent) while in the group of three cases which arose in the preauricular region, successful results were attained in two (66.6 per cent).

Effect of Metastasis on Prognosis.—Since no metastatic nodes were noticed on the first visit in any of the patients in this series no definite data is available

regarding the effect of initially diagnosed metastasis on prognosis. In three cases metastases were noticed some time after the initial treatment of the primary carcinoma. In one case an upper cervical mass was noticed three months after treatment of the primary lesion, but the patient refused lymphadenectomy and went to a faith healer. When she returned in six months the mass was inoperable, so roentgen ray treatments were given for palliation. In a second case the cervical metastasis was noticed six months after removal of the primary lesion, but a neck dissection was not recommended because of advanced age and poor general condition; palliative roentgen ray therapy was given. In a third case, metastasis had developed when the patient returned for belated checkup after eighteen months. Though the original carcinoma was in the preauricular region a new mass had appeared in the postauricular region.

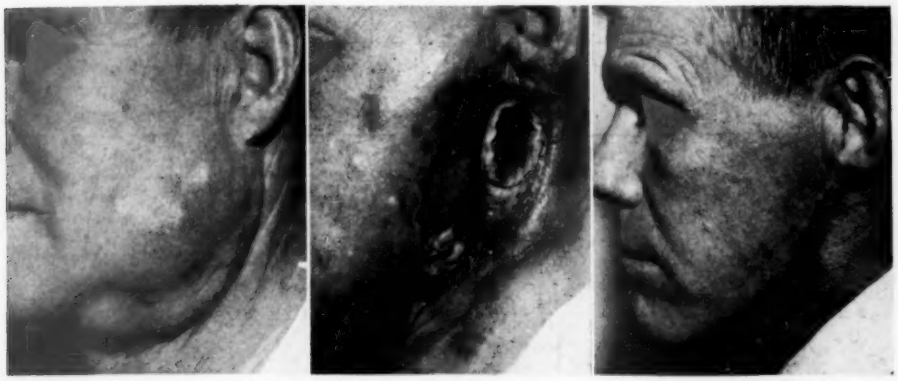

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FIG. 6.—(A) Benign mixed tumor of the parotid gland of 28 years' duration. It had been excised twice and the patient had received one course of six roentgen treatments. (B) Lesion after chemosurgical excision which required twenty-four days. The final layer of fixed tissue had separated except for one area under the ear where a rather deep, unpredicted extension of the neoplasm had been followed out. The protruding tissue in the lower part of the wound is normal submaxillary salivary gland tissue. (C) Healed lesion showing absence of facial paralysis except for the unimportant mandibular branch. There has been no evidence of recurrence after more than three years.

The latter was chemosurgically excised and the cervical nodes were excised by a member of the surgical staff. There was no evidence of recurrence after five years.

THERAPEUTIC RESULTS IN MIXED TUMOR OF THE PAROTID GLAND

Inasmuch as surgical excision of benign mixed tumors of the parotid gland is a fairly reliable procedure, most of the patients who entered this hospital with this condition were treated surgically rather than chemosurgically. For that reason this series includes the cases of only four patients who were chemosurgically treated. Successful results were attained in all four of these cases in the three-year period. In the five-year period there were two cases, and in both successful results were obtained. None of the patients had been previously treated. Two of the tumors were of large size (Figs. 5 and 6) while two were somewhat smaller with average diameters of 57 mm. and of 30 mm. Facial

nerve paralysis developed as a result of chemosurgical treatment in only one of the four patients (Fig. 6) and in this case it was the unimportant mandibular branch which was interrupted.

DISCUSSION

The chief advantage of the chemosurgical treatment of carcinoma of the parotid gland is the increased reliability which is attained by virtue of the systematic microscopic control of excision. The therapeutic results compare very favorably with those attained in other clinics by the use of ordinary surgical, electrosurgical and radiation technics (Table III). There is probably some degree of discrepancy in the comparison of the results reported from the various clinics because of differences in histologic interpretation. Thus, some workers consider almost all parotid tumors to be at least potentially

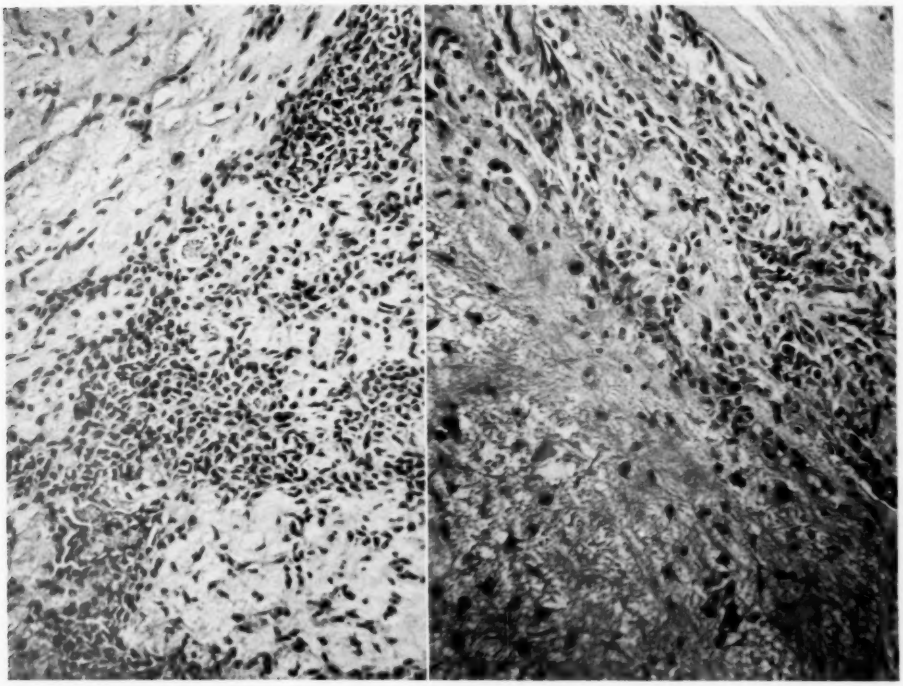
TABLE III.—*Comparison of the End Results of Chemosurgical Treatment of Carcinoma of the Parotid Gland with the End-Results of Other Treatments after Observation for Three Years or More*

Author	Treatment	Number of Determinate Cases	Successful Results	
			Number	Per Cent
Mohs	Chemosurgey	11	7	63.6
Ahlbom[12]	Surgery plus radium	81*	27	33.3
Swinton and Warren[13]	Surgery	6	2	33.3
Quattlebaum, Dockerty and Mayo[14]	Surgery (plus roentgen therapy in some)	19†	6	31.6
Martin[15]	Surgery (plus radium in some)	13	2	15.4
Stein and Geschickter[16]	Surgery	21	3	14.3
Benedict and Meigs[17]	Surgery	30	1	3.3
Wakeley[18]	Surgery	12	0	0
Janes[19]	Surgery	2	0	0
Martin[15]	Radiation	6	0	0

* Both the malignant and "semimalignant" neoplasms are included.
† Adenocarcinomas of "cylindroma" type only.

malignant, and therefore classify them all as carcinoma. Others consider only the highly anaplastic and actively invasive neoplasms to be carcinoma and classify the rest as mixed tumors. Some, Ahlbom[12] for example, take a middle stand and maintain that there are numerous borderline types which are not clearly benign or clearly malignant and which may be classified as semi-malignant. I find the last position is most consistent with my experience, and I feel that these "semi-malignant" tumors may justifiably be placed in the malignant group. Therefore, in the present series the neoplasms are considered malignant if they have definite infiltrative characteristics. While most of the cases fell quite distinctly into either the benign or malignant group, there were three carcinomas derived from mixed tumors, which might be classified as semi-malignant (*e.g.,* Fig. 4C & D). Since in two of these possibly doubtful cases unsuccessful results were obtained, there would be an increase in the rate of cure rather than a decrease if these cases were omitted from the series of malignant lesions.

Next to reliability the advantage of conservatism is most important. Since only 1 or 2 mm. beyond the level of neoplastic extension at any given point need be destroyed by the chemosurgical technic, it is possible to preserve a maximum amount of normal tissue. This is particularly important in regard to the facial nerve. In the present series of rather extensive carcinomas of the parotid gland, it seems likely that radical surgical extirpation would have produced complete facial paralysis in every case. By the use of the chemosurgical technic, however, it was possible to preserve the entire nerve in one case and to preserve part of the nerve in four others. In three cases there was



A B

FIG. 7.—Sections of mixed tumors of the parotid gland after fixation *in situ* by zinc chloride. (A) Tumor from patient shown in Fig. 5. (B) Tumor from patient shown in Fig. 6.

initial paralysis from previous treatment or from carcinomatous invasion. Less paralysis was encountered in the treatment of neoplasms in the lower retromandibular region than in the treatment of lesions in the preauricular region. However, one preauricular carcinoma was chemosurgically excised with paralysis of only the branches to the eyelid and forehead (Fig. 3). In three cases there was some return of nerve function after paralysis for periods of from one week to two years.

Both the reliability and conservatism exhibited by the chemosurgical treatment of carcinoma of the parotid gland are the results of the microscopic control which the technic provides. This microscopic control is needed because

most carcinomas of the parotid gland tend to send out grossly invisible extensions into the surrounding tissues. Thus, in this series, there were three neoplasms which had a strong tendency to follow the perineural lymphatics; in one case, the cancer cells extended in these structures for fully 5 cm. beyond the confines of the main tumor mass. In several cases the carcinoma followed for some distance along the perichondrium of the cartilages of the external auditory canal. In none of the cases of this series was the carcinoma limited to the parotid gland itself. Many of the extensions were so slender or the cancer cells were so intimately interspersed between the normal cells, that it was impossible to locate and remove them with any degree of accuracy without the microscopic control afforded by the chemosurgical method. I believe that the unpredictability of these outgrowths is the chief cause of the poor results obtained with radical surgical extirpation of the parotid gland. In retrospect it is clear that in every case of carcinoma in this series, the neoplasm extended in such a way that removal of the parotid gland alone would not have resulted in a cure.

Besides the advantages of reliability and conservatism, the low operative mortality is also an advantageous feature of the chemosurgical method. Thus, in this series there was only one death during the course of treatment. In that case the presence of an extremely extensive neoplasm in a patient who was in very poor general physical condition constituted a situation that led to fatal pulmonary edema and bronchopneumonia.

The chemosurgical technic is not without some disadvantages. The multiple stages required for the chemosurgical excision of an advanced neoplasm of the parotid are somewhat time-consuming for the operator and painful for the patient. However, since these advanced neoplasms probably would be fatal otherwise, these disadvantages seem relatively insignificant. Another disadvantage is that special training and constant practice with the technic are essential for the best results and a special clinic with provisions for the preparation of frozen sections of an unusual kind[10] is required.

SUMMARY AND CONCLUSIONS

The chemosurgical technic as used in the excision of tumors of the parotid gland is described and the therapeutic results in a series of thirteen carcinomas and four benign mixed tumors of the parotid gland are analyzed. The rates of cure in the series of patients with carcinoma of the parotid gland were 63.6 per cent in the three-year period and 60 per cent in the five-year period of observation.

All of the patients with benign mixed tumor of the parotid gland were successfully treated; there were four in the three-year period and two in the five-year period of observation.

The unprecedented reliability and conservatism of the chemosurgical method of excision are the results of the microscopic control which makes it possible to accurately follow out the "silent" outgrowths from the main tumor mass.

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RESECTION OF THE STERNUM FOR METASTATIC CARCINOMA*

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RESECTIONS OF VARIOUS PORTIONS of the sternum have been reported upon several occasions.[1, 2] The effects upon the cardiorespiratory systems that accompany instability of this large and important portion of the thoracic wall has limited the indications for its removal to malignant diseases affecting it. In previously reported cases, malignant diseases of the sternum requiring resection have generally been tumors arising primarily within it.[1, 2, 3] Few metastatic lesions in the sternum have been surgically removed.[2] Macey and Phalen,[4] in reporting two lesions of the sternum secondary to primary pulmonary adenocarcinomas, suggest that an attempt should be made to remove such lesions if they have not extended too widely. The usual contraindication is the presence of other osseous or pulmonary metastases.

It is the purpose of this report to describe the successful removal of a malignant tumor of the sternum, metastatic from a previously removed carcinoma of the breast, and the use of a large tantalum plate to restore immobility of this portion of the thoracic wall.

Case Report.—E. O., a 58-year-old white female, was admitted July 6, 1945, with a nodule in her right breast of several weeks' duration. Her history and physical examination was not unusual. Roentgenograms of her chest and spine showed no metastases. She was subjected to a right radical mastectomy on July 10, 1945. Subsequent split-thickness skin grafts were required to close the defect over her anterior thoracic wall. Histologic examination of the lesion showed a scirrhus and medullary adenocarcinoma infiltrating mammary fat. No lymph node metastases could be demonstrated.

Examination on January 13, 1948, revealed a 3 x 2 x 1 cm. hard, fixed tumor situated in the midline over the upper portion of the sternum. Roentgenograms of her chest and spine showed no metastases. A biopsy of the tumor showed adenocarcinoma of the same cell type as in the original lesion. Laboratory examinations demonstrated a mild anemia.

Operation: On January 31, 1948, under endotracheal nitrous oxide, oxygen, ether anesthesia, an incision was made over the medial one-half of each clavicle and inferiorly down to the xiphoid process, encompassing the tumor, which was located over the manubrium (Fig. 1 inset). Skin flaps were reflected upon either side exposing all the costal cartilages down nearly to the xiphoid process. Following a subperiosteal dissection of the clavicle upon either side, and using a Gigli saw, both clavicles were divided at the junction of the middle and proximal one-third. The first, second, and third ribs upon the right were then exposed subperiosteally and divided at the costochondral junction. The internal mammary vessels upon the right were ligated and divided in the first interspace. The loose fat and areolar tissue of the anterior mediastinum was then carefully dissected from the under surface of the sternum which was divided obliquely, through its body, from the third interspace upon the right to the second interspace upon the left. Both pleural cavities were opened and respiration was carried on with intermittent positive pressure. Following division of the first and second ribs upon the left, the lesion was removed

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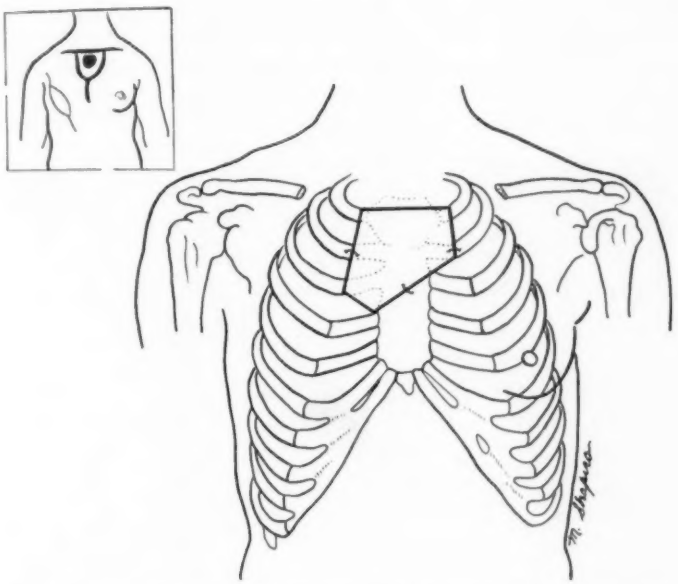


FIG. 1.—Diagram showing amount and location of the resected portion of the sternum and tantalum plate fixed in position.

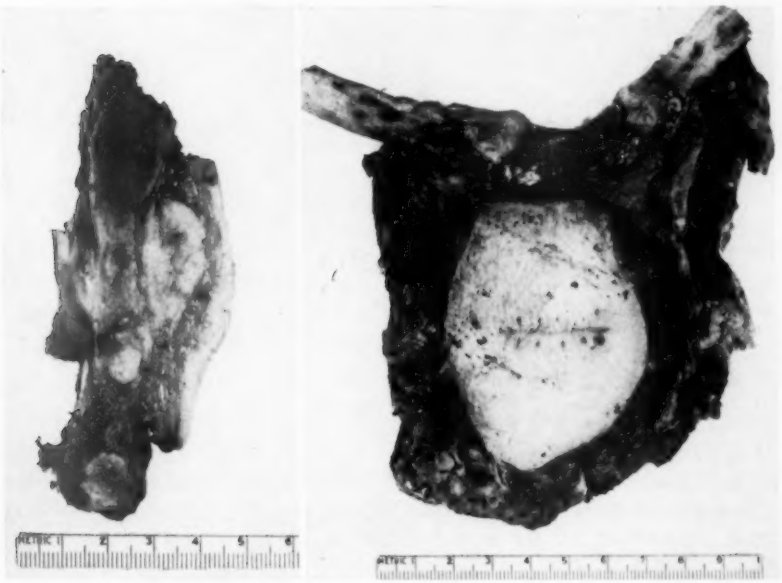


FIG. 2.—Longitudinal and frontal views of removed specimen after fixation in formalin. In the longitudinal view the lesion can be seen to extend completely through the sternum.

together with the proximal one-third of each clavicle, all of the manubrium, and approximately one-half of the body of the sternum (Figs. 1 and 2). The internal mammary vessels upon the left were divided and ligated. The rent in the pleura on the left side was easily closed with interrupted fine cotton sutures. The pleural defect upon the right, however, could not be closed in this manner. Accordingly, a large square of fascia lata was obtained from the right thigh, and sutured securely over the entire exposed anterior superior mediastinum, thus closing the right pleural defect. An intercostal catheter was

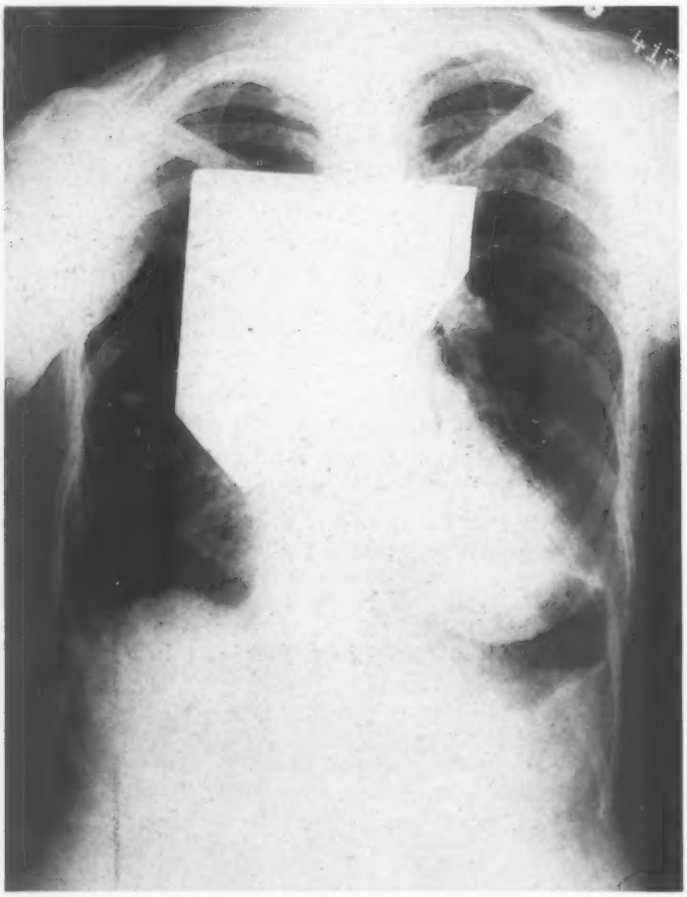


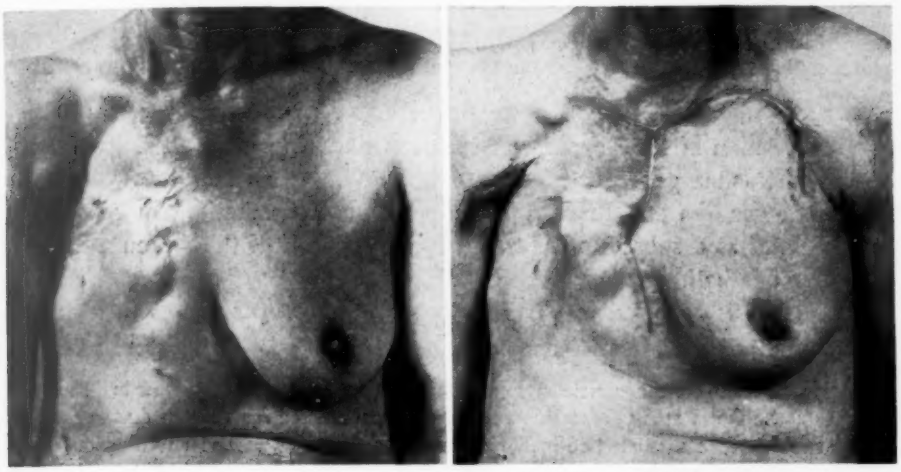
FIG. 3.—Roentgenogram made fourteen weeks following operation showing tantalum plate in position.

left in place in the fourth interspace upon the right. A large tantalum plate, 12.2 cm. wide, 14.0 cm. long, and 0.0375 cm. (0.015 inch) thick was fashioned to fit the bony defect. Each upper corner of the plate was mortised into the end of the first rib upon either side. Similarly, it was wedged into the second rib, but in addition was wired into place, using fine tantalum wire. A third wire fixed the bottom of the plate into the obliquely cut body of the sternum (Fig. 1). The plate, thus, seemed quite secure. The sternocleidomastoid and the sternal attachments of the ribbon muscles of the neck were sutured to the upper aspect of the pectoralis major upon the left, and to the subcutaneous tissue upon the right. Because of the defect in the skin, occasioned by excision of the skin overlying the tumor, it was necessary to rotate a flap of skin and subcutaneous tissue from the left side. The skin and subcutaneous tissue was closed in two layers with fine No. 60 cotton. Penrose

drains were left under the skin for 48 hours. The patient received 1500 cc. of whole blood during the procedure.

Postoperative Course. Her convalescence was quite uneventful. Small hematomata were aspirated from beneath the skin occasionally for three weeks, following which the wound appeared to be well healed with no evidence of an accumulation of serum or blood beneath the skin or plate. Forcible respiration does not buckle the plate. At the date of this writing, the plate remains securely in place eight months after operation, and causes no discomfort to the patient. There is no evidence of other local or distant metastases.

Comment: The surgical removal of metastatic carcinoma anywhere in the body must be considered a palliative procedure. Occasionally, however, such lesions appear to be unaccompanied by similar ones and the patient may survive for many years.[5, 6] However, the prediction cannot be made that such a fortunate recovery will occur in any specific instance. The selection of cases



A B

FIG. 4.—A. Before operation showing site of metastatic lesion. B. Photograph taken approximately five months after operation.

for removal of isolated metastases can only be made after determining that a) the general condition of the patient is good, b) there is no evidence of other metastases in the same or other systems, and that c) the lesion can be completely removed by a procedure unaccompanied by a prohibitive mortality.

Tantalum, a metal proven to be inert in human tissues, has recently received attention in the repair of bony defects, chiefly in the skull.[9, 10] In addition, it has been used as wire, wire mesh, and tubes for arterial anastomoses. Paulson[7] has used tantalum plates to cover chest wall defects but abandoned the method because of difficulty encountered in immobilizing the plate on a constantly moving structure such as the thorax. Griswold,[3] in 1947, reported the successful temporary use of a tantalum plate as a prosthesis following resection of the body of the sternum for an osteochondrosarcoma. He found it necessary to remove it approximately two and one-half months later because of recurring hematomata. Griswold concluded that the method was a satisfactory procedure for a temporary readjustment period following operation.

A review of some anatomic facts may explain the successful use of the tan-

talum plate in the case reported. 1. There is no motion between the first rib and the manubrium for a joint does not exist at this point. 2. The second to the seventh ribs, inclusive, articulate directly with the sternum by means of true joints lined with synovial membranes. 3. The seventh to the ninth ribs move between each other by means of interchondral articulations, but are anchored to the sternum through the sixth and seventh costal cartilages. Thus, it is seen that the removal of the upper one-half of the sternum requires the sacrifice of only a few joints (in the case reported, three) and fixation of the ribs and sternum to a metal plate is correspondingly easier. On the other hand, the substitution of a metal plate for the lower one-half of the sternum requires it to be an anchoring post for twelve or fourteen ribs. Complications incident to motion of so many ribs upon a metal plate are easily understood. Such a plate substituting for a portion of the sternum should probably then be limited to the superior portion of this structure, unless it is to be used, as Griswold suggests, as a prosthesis for a temporary postoperative period of readjustment.

SUMMARY

1. Resection of the sternum for metastatic carcinoma in carefully selected cases is a feasible procedure.

2. The use of a tantalum plate as a permanent prosthesis is more likely to be successful as a substitution for the upper one-half of the sternum than for the lower one-half.

3. A case is reported in which such a procedure was successfully accomplished.

ADDENDUM: Since this article was submitted for publication, this patient has been seen monthly in the Out-Patient Department. She was hospitalized for 12 days during October, 1948, at which time a small two-inch full thickness flap of skin and subcutaneous tissue was rotated over the right edge of the plate. She was last seen January 25, 1949, one year after operation, at which time there was no evidence of recurrence or metastases and the prosthesis was solidly in place.

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HYPERNEPHROMA METASTATIC TO THE THYROID GLAND

Report of a Case*

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Hypernephroma metastatic to the thyroid gland is so rare that only 20 cases are reported in the literature up to 1947. Linton *et al*[1] in 1946, in an extensive review of the literature, found only 15 proven cases and added one of their own. In 1947 Boys[2] also reviewed the literature, found 15 cases and added a case report. Each of these authors in his review found reported cases not mentioned by the other. A summary of these reviews is presented in Table I.

CASE REPORT

L. E., a man aged 48 years, was admitted to Albany Hospital on April 7. 1942, with a chief complaint of fatigability, weight loss and the presence of a lump in the neck of 5 months' duration.

About 5 months before admission the patient first noted a lump in the front of his neck which had not noticeably changed in size. During this time he experienced increasing fatigability and listlessness. In the few weeks prior to admission he became completely exhausted each day within one hour after arising in the morning. Although his appetite remained unchanged he lost 20 pounds in weight. He had increasing bouts of palpitation unassociated with dyspnea or ankle edema. Although considered a nervous individual he did not complain of any change in this respect but did admit being more easily upset. He perspired freely but did not like cold weather. Review of systems disclosed no abnormalities other than the presence of nocturia 3 times per night.

The past history revealed that 8 years previously, on May 18, 1934, he had a right nephrectomy. A tumor in the right kidney was reported by the pathologist to have been a hypernephroma. During his convalescence a course of deep roentgen-ray therapy was given in another city. This treatment caused transient fatigue and low back pain. Roentgenograms of the spine and of the pelvis in 1935 revealed no metastases. For one year after nephrectomy the patient complained of urinary frequency and burning. Eighteen months after operation, the patient was symptom free, had gained weight and felt completely well. He was checked in the Out-Patient Clinic every 6 months for 2 years and once a year up to May 10, 1941. There were no further complaints until onset of symptoms 5 months before second admission.

There was no family history of goiter, diabetes, nor tuberculosis.

The patient was a well-developed man with evident recent weight loss. The temperature was 97°, pulse 100, respirations 22, and blood pressure 104/68. The left pupil was slightly larger than the right but both reacted to light and on accommodation. The extraocular movements were normal. There was no exophthalmos nor widening of the

* Submitted for publication, November, 1948.

palpebral fissures. The trachea and larynx were deviated to the left by a visible mass in the right side of the neck. The right lobe of the thyroid gland was enlarged, nodular, and contained one, large, particularly hard nodule at the lower pole. The left lobe was slightly enlarged but not otherwise remarkable. The large nodule in the right lobe moved freely on deglutition. There was no thrill nor bruit.

The lungs were clear to percussion and on auscultation. The heart was not remarkable except for a few extra systoles. There was a well healed nephrectomy scar in the right flank. The liver was percussed 3 fingers below the costal margin.

A roentgenogram of the chest revealed no evidence of metastases to lungs; the heart was slightly enlarged. Hemoglobin was 17 Gm., red blood cells 6.63 million, color index .9, white blood cells 9,700 with 76 polys, 1 basophil, 20 lymphocytes, 3 monocytes. Platelets appeared normal. Urinalysis revealed no abnormality. Blood Wassermann negative.

Diagnosis—Non-toxic nodular goiter. The possibility of a metastatic hypernephroma or other malignant lesion of the thyroid gland was considered.

TABLE I

	Author	Year Reported	Number of Cases
1.	Lubarsch	1894	1
2.	Kodzubowski	1904	1
3.	Barjon and Janitot	1912	1
4.	Rost	1912	1
5.	Pistocchi	1922	1
6.	de Quervain	1924	1
7.	Klose	1925	2
8.	Kolodny	1926	1*
9.	Willis	1931	1
10.	Pemberton and Bennett	1934	2
11.	Caylor and Caylor	1936	1
12.	H'Doubler	1936	2
13.	Weiskittel	1937	1
14.	Fey and Truffert	1938	1
15.	Welti and Huguenin	1939	1
16.	Long and Black	1945	1
17.	Linton, et al.	1946	1
18.	Boys	1947	1

* Questioned by Linton.

On April 9, 1942, subtotal thyroidectomy was performed. Anesthesia was novocaine infiltration, supplemented by nitrous oxide and oxygen inhalation anesthesia. The thyroid was exposed through a low collar incision with midline division of the pretracheal muscles. The right lobe of the thyroid was first elevated into the incision and found to be the site of hypertrophy with multiple, small, adenomata. The superior pole lay posterior to the trachea. The nodular masses were removed by resection of the right lobe and the capsule was closed. The left lobe was found to be the site of a similar change and the same procedure was carried out as on the right. The wound was closed without drainage. The patient withstood the operation well and made an uneventful recovery.

Dr. A. W. Wright, head of the Department of Pathology, gave the following report on the tissue excised:

Gross Description. The specimen consists of one large and four small masses of thyroid gland which weigh together 24 Gm. All of the masses are composed of dark reddish, typical thyroid tissue which is somewhat nodular with moderate amounts of colloid. The largest mass contains, in addition, a fairly large, well outlined, pinkish-yellow, soft, homogeneous nodule which stands out from the adjacent thyroid tissue. Other smaller but

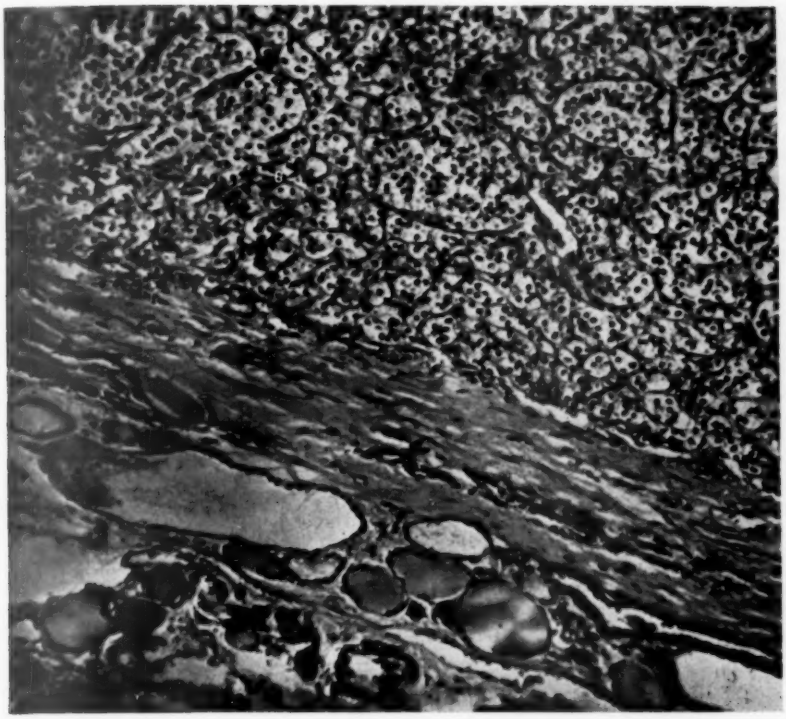

FIG. 1.—Metastatic clear cell carcinoma of kidney origin occurring in thyroid gland.

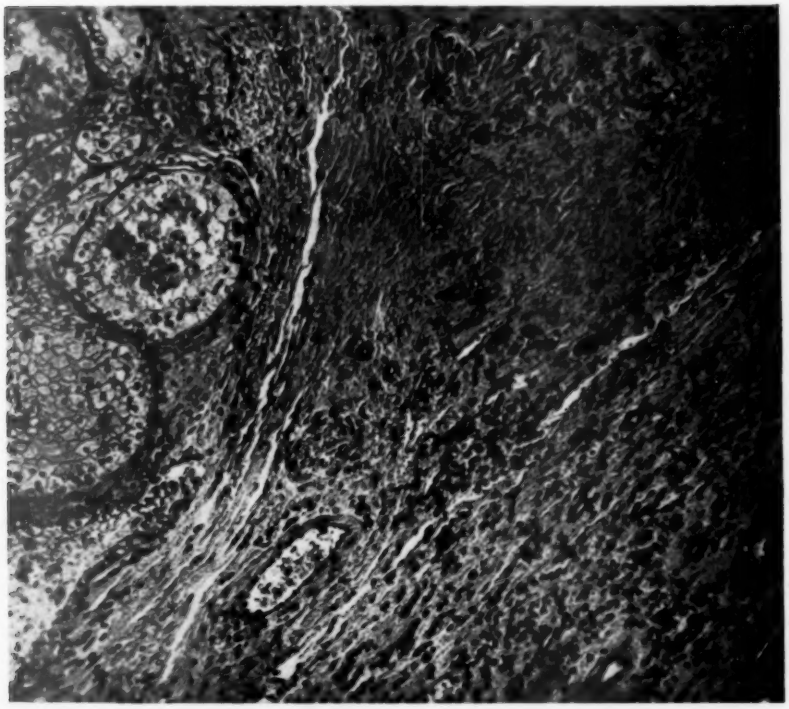

FIG. 2.—Primary clear cell carcinoma occurring in right kidney.

otherwise similar nodules are present elsewhere in the largest thyroid mass and in most of the smaller ones.

Microscopic Description. Sections from this thyroid gland (Fig. 1) show an adenomatous colloid goiter which is composed of small and large acinar groups, all of which contain colloid. The lining epithelium is generally low or flat.

In one section a totally different type of lesion is present. It is a fairly large, well outlined focus of neoplastic epithelial tissue which is composed of atypical cells growing in cord-like or alveolar fashion, often with lumens. In the latter situations the cells are oval or polyhedral in shape with distinct thin cell membranes and clear cytoplasm. Indeed, they appear to be little more than an empty space surrounded by a cell membrane. Each cell contains a dense spherical hyperchromatic nucleus which is centrally located, suspended, as it were, in an empty sac. Several large venous channels, into one of which a small tongue of tumor tissue projects, are present. About the periphery of the neoplastic focus there is a narrow, partially hyalinized, fibrous capsule which encircles part of the growth. This tumor is not characteristic of any primary thyroid carcinoma. Because of its strong resemblance to a primary renal carcinoma it is considered to be a metastatic clear cell carcinoma of renal origin.

Re-examination of the sections of the kidney (Fig. 2) removed surgically from this patient in 1934 discloses the presence in that organ of a typical primary clear cell carcinoma. The neoplastic cells have clear cytoplasm, thin, distinct cell membranes, centrally placed hyperchromatic nuclei, and grow in cord-like or tubular fashion. The cells of the thyroid tumor resemble these renal carcinoma cells so strikingly that the present nodules in the thyroid are undoubtedly metastases from the primary renal growth.

Subsequent Course. According to information received from the family physician, a growth as large as two fists appeared in the left side of the abdomen. Shortly after the appearance of this abdominal mass, death occurred, May 19, 1943, 13 months after thyroidectomy and nine years after removal of the kidney tumor. Permission for post-mortem examination was denied.

DISCUSSION

The case reported is one of six now in the literature in which metastatic hypernephroma appeared in the thyroid gland several years after nephrectomy for renal carcinoma. The metastatic nature of the thyroid lesions was, in each instance, discovered 7 to 13 years after removal of the renal tumor. In the case presented by Linton *et al*[1] the presence of hypernephroma in the remaining kidney at the time of thyroidectomy makes the primary source of the metastasis doubtful but in the other five cases the source could only have been the original hypernephroma.

Many of the cases reported were found only on necropsy. Since the thyroid gland is not routinely removed at many autopsies, it is reasonable to assume that more cases of metastasis to the thyroid gland from renal carcinoma have occurred than have been reported.

Because of the limited number of cases reported, no conclusions can be drawn. However, a metastatic hypernephroma must be seriously considered in those patients who develop a goiter following a diagnosis of hypernephroma. Since such metastases are known to have occurred as late as 13 years after excision of the original renal tumor, not even the passage of many years following the primary operation should rule out the possibility of such a diagnosis.

SUMMARY

A detailed case report of metastatic hypernephroma to the thyroid gland is presented and 20 cases found in the literature tabulated.

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RETROGRADE INTRAGASTRIC INTUSSUSCEPTION OF THE JEJUNUM FOLLOWING SUBTOTAL GASTRECTOMY*

REPORT OF A CASE, APPARENTLY THE SECOND SUCH IN THE LITERATURE

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RETROGRADE INTUSSUSCEPTION of the jejunum following subtotal gastrectomy is so rare as to be a medical curiosity. A search of the literature reveals only one comparable case. It was reported by McNamara in 1944.

Case Report.—JKW, white, male, age 55, was seen first on December 26, 1945. His chief complaint was stomach trouble. It began 18 years ago characterized by bloating and epigastric pain which was relieved by soda. His first hemorrhage occurred 13 years ago, the vomitus had a coffee ground appearance and the stools were tarry for several days. In recent months the patient experienced severe heart burn and often vomited small amounts of sour material with relief. On November 16, 1945, he had a gastric hemorrhage and was given a transfusion of 1,000 cc. of blood. Pain and discomfort became more frequent after the hemorrhage, and was the reason for the patient entering the hospital. Roentgenograms over a period of years, done in Lexington and elsewhere, revealed a duodenal ulcer. In addition, during the past year the patient had nocturia 3 to 4 times and some dribbling. Eighteen years ago he had had a left inguinal hernia repaired and left orchidectomy, probably for an undescended testis. There was a recurrence of the hernia 6 years later. Appendectomy had been done 17 years ago. On 12–27–45, a subtotal gastrectomy was done by me for a recurrent, bleeding, chronic duodenal ulcer, and posterior Polya type of anastomosis was done. Convalescence was uneventful.

The patient re-entered the hospital 4–12–48 on the urological service of Dr. Douglas Scott, at which time his chief complaint was gradually increasing urinary frequency and difficulty in voiding. Since his stomach operation, he had only an occasional episode of upset stomach with slight vomiting. Urologic investigation revealed a bladder capacity of 8 ounces without residual. The K.U.B. was negative, B.U.N. 19 mg.%, Rbc. 4.6 million, Hgb. 91%, urine negative. On 4–15–48 at 8:35 A.M. the patient went to the operating room for a transurethral resection. Spinal anesthetic was induced with 8 mg. of procaine in glucose and spinal fluid between the 3rd and 4th lumbar vertebrae. One-quarter cc. of neosynephrin was given, hypodermically, at the same time. The systolic B.P. ranged from 110–124—92–112 during the operation. A trilobar enlargement with ball-like median lobe was found. Twenty-seven grams of benign tissue was removed and a right vasectomy was done. Before the operation was completed the patient became nauseated and retched violently several times. Vomiting persisted at frequent intervals after the patient returned to his room. The vomitus was at first dark reddish-brown and later appeared to be bloody. This was accompanied by severe cramping pain localized to the U.L.Q. It was not relieved by morphine, ¼ grain. I saw the patient the following afternoon and examined him at 4 P.M. He stated that since his stomach operation he had been relatively free from indigestion except for occasional nausea and vomiting of clear material and infrequent heart burn.

Examination revealed an acutely ill patient. His skin was pale and clammy. He was vomiting small amounts of dark bloody, odorous material at frequent intervals and complaining of severe cramping pains in the U.L.Q. The temperature was 97°; the pulse was 90, regular and of good quality. The B. P. was 108/88. The abdomen in this rather

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thin man was scaphoid and soft with slight tenderness in the U.L.Q. There was no rigidity, masses, or palpable organs. Upper right rectus, lower right rectus and left inguinal scars were present with a hernia in the latter. Clear urine was passing freely from the indwelling catheter. The R.B.C. was 4.9 million and the Hgb. 91%. Wangensteen suction was started and afforded the patient immediate relief. Blood, glucose, vitamins and amigen were given intravenously. For the next six days the patient continued to vomit at irregular intervals in spite of the indwelling intragastric tube which was in place most of the time. The vomitus was always a dark, foul, bloody material. The (R) temperature ranged from 99^6 to 100^2. The pulse approximated 110. On 4-20-48 the leucocyte count was 18,100 with 72 polys. On 4–23–48 a barium meal was given which revealed a greatly dilated

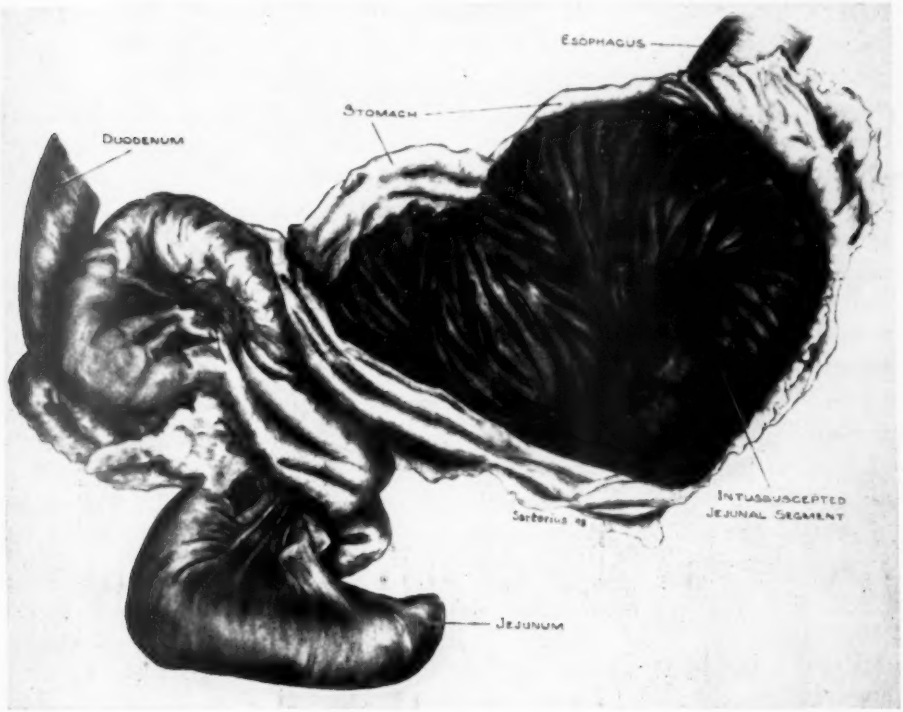

FIG. 1.—Postmortem specimen shows the opened stomach with the intussuscepted jejunum.

stomach of which the distal half had been removed. There was a deformity which suggested a penetrating ulcer at the junction of the jejunum with the stomach. The 5-hour film showed 90% gastric retention.

On 4–24–48 the patient's condition became worse and an enterostomy was done under local anesthesia through a small upper left rectus incision. Feedings of milk, custard and amigen were given through the tube at 2-hour intervals. The patient's condition was unimproved and vomiting continued. On 4–27–48, in spite of four transfusions of 500 cc. each of blood, the R.B.C. was 3.4 million, the Hgb. was 65%, the Wbc. was 24,900 with 84% polys. At 5:30 P.M. the abdomen became very tender, rigid and distended in the upper one-half. The pulse became weak and imperceptible, the skin cold and clammy and the patient died at 11:50 P.M.

Autopsy.—The abdomen was somewhat distended. On opening the peritoneal cavity there was found four or five hundred cc. of turbid, coffee colored fluid. Peritonitis extended from the pelvis to the under surface of the liver. The stomach was greatly

enlarged and when palpated a rough, soft mass could be felt within the lumen. The lower half of the stomach had been resected, and when the stomach was opened a large brownish-black corrugated mass was seen. A retrograde jejunogastric intussusception of the efferent portion of the jejunum had occurred through the gastrectomy stoma, making a cylindrical mass measuring 17 cm. in length and from 6 to 8 cm. in diameter. The distal end was necrotic and dark in color. The portion of the small intestine below the intussusception was grossly negative. The site of the recent prostatic transurethral resection was not unusual.

Discussion.—Intussusception is usually considered a disease of infants and young children. In these age groups it is one of the most important surgical emergencies. The process is often progressive and frequently without known cause. In adults the condition is usually brought about by some mechanical abnormality. In all age groups the direction of the intussusception is usually descending. According to Baumann there is one ascending to 200 descending types. In 1923 Drummond called attention to retrograde intussusception of the jejunum following gastro-jejunostomy. He reviewed the 11 cases previously recorded in the literature; two in England, nine on the Continent, and added his case which made 12 in all. His chief interest in the problem lay in the difficulty in explaining why it should occur in a few cases only and what steps could be taken in preventing it, or its relapsing as in the case of Baumann. He thought that occasionally rapid emptying of acid gastric content into the jejunum might result in forcible antiperistaltic action. The type of gastro-jejunostomy seemed to be of no consequence. In the first 12 cases reviewed, five were the anterior type, five were posterior type and no mention was made of the type in two cases. Enteroanastomosis had been done in five of the 12 cases. With the increasing popularity of gastro-jejunostomy in the treatment of peptic ulcer by 1935, Debenham was able to collect 35 cases of retrograde intussusception of the jejunum and added a case to the series. He was surprised that this complication was not reported until 1917, although gastro-jejunostomy was first performed in 1881. In the recorded cases the incident occurred from six days to 16 years after the original operation. The length of involved segment varied from 4 cms. to 2 metres and the type and size of the stoma apparently played no part in initiating the process.

Chesterman thought that the condition was of sufficient interest to warrant record by virtue of its rarity, the ease of diagnosis if its possibility is remembered, and the hopeless prognosis without early surgical intervention.

According to the collected reports the symptoms seem to follow a rather definite pattern. Following at variable periods after gastro-jejunostomy there is a sudden onset of cramp like upper abdominal pain which frequently doubles the patient up. This is followed by vomiting, first of food and bile and then bloody fluid. As the pain and vomiting continue the patient's skin becomes pale and clammy. Rigidity and distention do not appear early, nor is tenderness constant. The presence of a soft tumor in the upper abdomen has been noted in about one half of the reported cases. Early surgical intervention with reduction of the intussusception, or resection has yielded good results.

Sufficient interest has been aroused and attention focused on retrograde

jejunogastric intussusception so that each year finds new cases added to the increasing number recorded in the literature. A very careful search, however, reveals but one case comparable to the one I report. In 1944, McNamara reported the first case of retrograde jejunogastric intussusception through a subtotal gastrectomy stoma. So far as I can determine, the present case is the second such appearing in the literature. The etiology is speculative. However, since the onset was sudden and acute during an operative procedure one is inclined to carefully evaluate the anesthetic and the operation for contributing or precipitating influence. It is an accepted fact that patients receiving a spinal anesthetic may become nauseated and vomit. A transurethral resection rarely, if ever, initiates vomiting. I believe it more reasonable to attribute the vomiting in this patient to the anesthetic agent. Since it was so violent it is most likely that it was the influence in precipitating the retrograde intussusception. The repeated vomiting indicated a high obstruction, but the cause of the foul, bloody vomitus was erroneously deduced. In view of the past history of gastric resection for a bleeding ulcer and the subsequent, although mild recurrence of dyspepsia, the condition was first attributed to an obstructing, bleeding, marginal ulcer. Because of the high resection the remaining segment of stomach was beneath the thoracic cage and a tumor was never felt.

The explosiveness of the symptoms in the now two reported cases of retrograde jejunogastric intussusception through the gastric stoma are quite similar to the same process in the more frequently occurring intussusception following gastro-jejunostomy. Characteristics are the sudden onset of severe cramping abdominal pain, persistent vomiting of bloody material, shock and in some cases the presence of a soft tumor in the upper abdomen. If the condition is known and its possibility is remembered the diagnosis should not be too difficult. The prognosis is hopeless without early surgical intervention.

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WANDERING SPLEEN*

REPORT OF A CASE COMPLICATED BY A TRAUMATIC CYST

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WANDERING SPLEEN IS VERY RARE, as shown by statistics of a large number of splenic diseases published by various authors. Whipple (1945)[33] reported a series of 1,437 cases of splenic diseases seen at the Combined Splenic Clinic of the Columbia Medical Center over a period of 10 years; the series included about 20 different diseases of the spleen, but not a single case of wandering spleen. Among 1,003 splenectomies done at the Mayo Clinic over a period of 40 years (1904–1945), wandering spleen was present in two cases only, and both occurred before 1934.[13, 25] Most of the reported cases were complicated by torsion of the splenic pedicle, and the following case is interesting as it shows the association of another complication, so far not reported in the literature, namely, traumatic subcapsular blood cyst.

CASE REPORT

S. S. J., female, aged 51 years, married, had 2 children, was admitted to the University Hospital, Alexandria, on Nov. 11, 1946, complaining of a mobile swelling in the left side of the abdomen, continuous dragging pain in the region of the stomach, sense of distention, occasional attacks of vomiting following heavy meals by 1 or 2 hours, (the food being vomited unchanged), and splashing sounds in the stomach after drinking water. These symptoms were present for the last 4 months. Five months before the date of admission, *i.e.*, one month before the onset of the present complaint, she was kicked in the left upper part of her abdomen by a donkey, the kick was so severe that the patient fell on her back, hit her head on the ground, lost consciousness, and was carried home. She came around 2 hours later, and immediately after that she felt severe colicky pain at the site of the trauma associated with frequent vomiting, the first vomit contained red blood. For the following 3 days the patient was in a semidrowsy state, and the vomiting and pain continued. She was forced to stay at home in bed for 13 days, after which her condition improved gradually. No signs of injury of the abdominal wall at the site of the trauma was noticed by the patient. One month after the date of the accident she first noticed a small mobile swelling below the left costal margin, which was slightly tender to her touch. The swelling gradually increased in size, and was associated with repeated attacks of localised pain which radiated to the left loin. The dragging sensation and the gastric discomfort developed gradually. The general health of the patient suffered as a result of restricting her diet so as to avoid the vomiting and the pain. Nothing of importance was found in her past history except that four years ago she developed an irregular fever which persisted for about one month, the fever subsided without medical treatment, and did not recur. After a short time she noticed ill-defined pains in the left hypochondrium which passed off within a few days. She was quite normal up to the date of the accident. The family history is of no special importance.

Physical Examination: showed a moderately built and nourished female subject, with normal features; P: 80, T: 37, R: 24, B.P.: 150/100. The abdomen showed redundant and inelastic skin in the lower half, flabby and weak muscles, wide subcostal angle, and absence of dilated or varicose veins in the abdominal wall. There was a swelling easily

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seen by inspection while the patient was standing, but better still when she was lying on her back. The swelling occupied the left lumbar, lower part of left hypochondriac, and left part of umbilical regions; it was globular, 15 cms. in diameter, cystic with free fluctuation, smooth on the surface, and with a definite contour. On deep palpation, it was found that this cystic swelling overlay and was fixed to an enlarged spleen, the lower pole of which reached the left iliac fossa, while the rounded upper pole was felt below the left costal margin and was easily grasped by the hand. The anterior border of the spleen was sharp, with two notches on it, while the posterior border was rounded, smooth, easily felt, and it was possible to lift the whole spleen up by insinuating the hand behind it. The cyst and the spleen moved with respiration, and it was possible to move them together to the right side of the abdomen until they filled the right lumbar region, where they stayed for a while, then gradually returned to the left side. This movement was painless. When the patient lay on her right side the swelling fell beyond the middle line. The spleen was movable down so far that its lower pole disappeared behind the symphysis pubis, but it was not possible to push it up beneath the costal margin as the cyst bulged very much anteriorly. The cyst was slightly tender on deep pressure, dull on percussion, but loops of small intestine came in front of the spleen to surround the cyst, so the rest of the splenic surface was resonant. The area of normal splenic dullness was absent. A band of resonance was found between the upper pole of the spleen and the costal margin, and a similar area was detected between its posterior margin and the outer border of the left sacrospinalis muscle. The liver was firm, smooth, and its lower border felt 4 fingers below the xiphoid process, and the upper border was in the fifth intercostal space (*i.e.*, the liver was not ptosed). The lower pole of the right kidney was palpable, and the rest of the abdomen was free. It was evident that the spleen had altered its relations so that its diaphragmatic surface now faced antero-laterally, and its anterior and posterior margins faced medially and laterally respectively. The case was diagnosed enlarged wandering spleen, with a traumatic subcapsular cyst on the diaphragmatic surface. Splenectomy was decided upon.

Laboratory Data.

Urine: acid, alb.+, sugar—, pus cells++, Bilh. ova+.

Stools: positive for ascaris ova.

Blood urea: 38 mgs.%

U.C.T.:			
	fasting before urea—		0.6 Gm.%
	first hour	90 c.c.	0.8 "
	second hour	110 c.c.	1.0 "
	third hour	100 c.c.	1.2 "

Blood picture: Hb: 70%, R.B.C.: 3,900,000; W.B.C.: 5,400; (eos. 7%, polym. 58%, mono. 30%, bas. 0%) negative for malaria.

W.R.: neg.

Radiography: Stone pelvis of left kidney, (this was found to have passed to the ureter after 6 months).

No definite soft tissue shadow of the spleen, or of the cyst was seen in a plain roentgenogram of the abdomen. No signs of calcification in the cyst. Thorotrast injection was not done, nor a barium meal or enema.

Operation: Dec. 15, 1946, by Prof. Abbas Hilmy.

Blood transfusion of 1,000 cc. was given before the operation. Under light percaine spinal anesthesia the abdomen was opened by a left upper paramedian incision. On opening the peritoneum the anatomy of the condition was obvious. The spleen was found in the centre of the abdominal cavity, its costal surface turned forward, and over it, near the lower pole, a big brown coloured cyst with smooth shining wall. The cyst was tense and measured about 15 cms. in diameter. The surface of the spleen was smooth, and its upper pole lay well below the left costal margin. No adhesions were attached to the

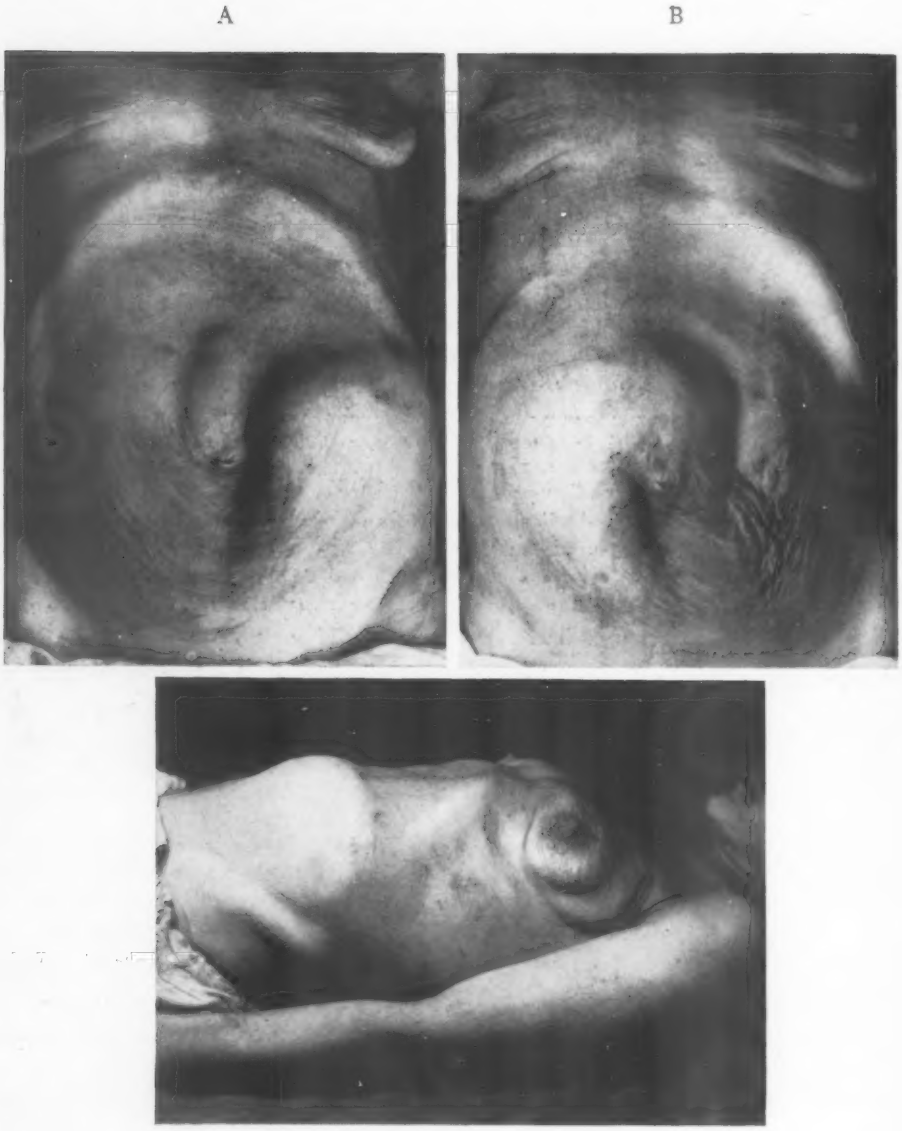
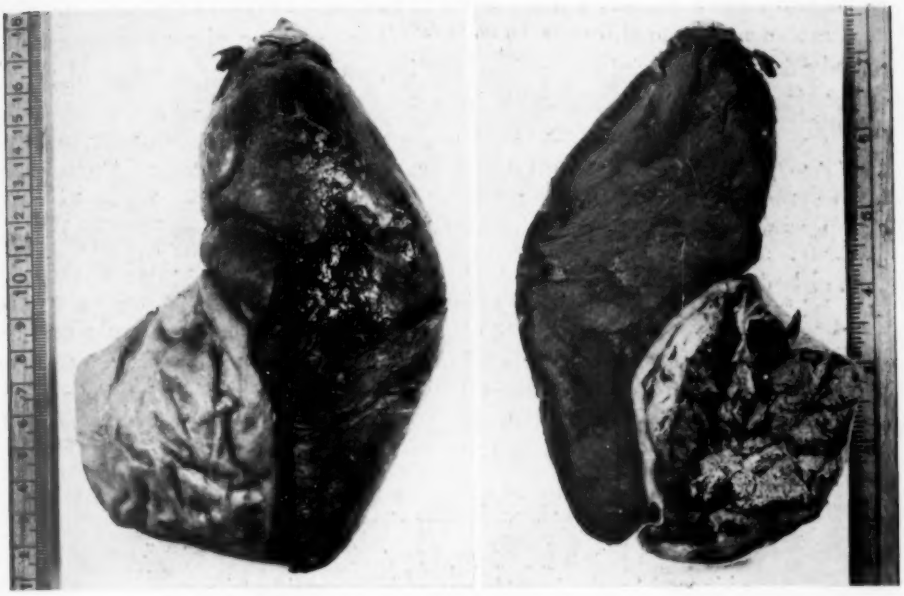


FIG. 1.—Photograph of patient before operation. A: Splenic cyst in the resting state, the patient lying on her back. B: The spleen has been pushed to the right side of the abdomen, and the picture taken immediately after the hand was removed. C: Lateral view of the abdomen to show the bulging of the cyst anteriorly; it was not possible to push the spleen back under the costal margin.

spleen, except for the thin stretched phrenico-splenic ligament, which was cut and the spleen easily delivered. The splenic pedicle was long, thin and broad, and the tail of the pancreas was free from it. The gastro-splenic ligament was longer than usual, and was cut between ligatures. The main pedicle was excised in sections between ligatures on the proximal side, and clamps on the splenic side. After the spleen was removed with the clamps on, the ligatures on the pedicle were reinforced by another series of similar ones. The rest of the abdominal organs were inspected and were found normal except for the stomach which was dilated and ptosed, and the transverse colon which was unduly



A B

FIG. 2.—Specimen of the spleen with the cyst on the lower part of the costal surface; the picture was taken after the spleen has been hardened in formalin, showing a relative reduction in its size. A: Costal surface. B: Cut section.

mobile. The stone in the left kidney was not dealt with, and the abdomen was closed in the usual manner. The removed spleen weighed 1,200 Gm., it was 25x15x15 cm. in dimensions, the diameter of the cyst 15 cm., and contained about 300 cc. of a thin brownish fluid. The inside wall was full of fibrinous trabeculae.

The patient passed through a smooth uncomplicated postoperative course, and was discharged fit on the 12th day, with a good sound scar. She was seen 2, and 16 months after the operation, was found to be in very good health, and her previous complaints completely disappeared.

Pathologic Report (By Prof. Gazayerly). Spleen (after evacuation of blood and being hardened in formalin) weighs 750 Gm., there is a cyst about 7 cm., containing fibrin, and some blood. The peripheral wall of the cyst is very thin and about 1 mm. thickness but where it is attached to the spleen over an area of 8 cms. the wall is thick (0.5 cm.); and is made of greyish white fibrous tissue. On section the splenic tissue is deeply congested and the Malpighian bodies are rather inconspicuous. Microscopical examination showed that the white pulp is greatly encroached upon by the congested red pulp. The sinuses of the red pulp are distended with blood. The splenic arterioles show

marked thickening of their walls with hyaline degeneration. The wall of the cyst is made of fibrous tissue. The picture is consistent with Egyptian splenomegaly and a blood cyst. It is quite possible that the blood cyst has resulted from an organised hematoma.

COMMENT

This case is interesting because it presents the two most uncommon conditions of the spleen, namely, the wandering state and cyst formation. The enlargement is due to the condition called Egyptian splenomegaly, an endemic disease in Egypt, related etiologically and pathologically to bilharzial infection of the alimentary canal.[1, 14, 18, 19, 20, 26, 29] It is one type of congestive splenomegaly due to bilharzial cirrhosis of the liver, the spleen as a result of portal congestion undergoes considerable hypertrophy. Such spleens always tend to get fixed in position by a process of perisplenitis giving rise in some cases to very dense adhesions between the spleen and the diaphragm. During the operation of splenectomy these must be cut by the hand, scissors, or between clamps; some cases are even impossible to remove on account of a process of complete cohesion between the spleen and its bed. The condition usually remains silent until the spleen is so enlarged as to produce signs and symptoms due to its mechanical effects. The organ is usually fibrous and firm; rupture of Egyptian splenomegaly is therefore rare as compared with rupture of malarial spleens. The enlargement in this case was associated with a good range of abnormal mobility which saved the spleen from a complete tear as a result of the comparatively severe kick, (a trauma which most probably would rupture a normal spleen, or more easily an enlarged fixed one). An anterior subcapsular rupture occurred which organised into a hematoma; within four months this developed into a false blood cyst. The stomach also suffered from the kick as evidenced by the hematemesis. The resultant increase in weight of the spleen increased its range of mobility and started the various symptoms which were mostly due to the mechanical dragging on the stomach. It is questionable whether the trauma had directly affected the mobility of the spleen by tearing its supporting ligaments.

DISCUSSION

The normal spleen has a very limited range of mobility. Fowler[12] has studied this in many laparotomies, and found that the normal spleen has excursions not exceeding 1½ inches. The factors which keep it in its usual place in the upper abdomen are the general intra-abdominal pressure, and the various peritoneal reflections or ligaments which fix it to the surrounding structures. The two chief and strong ones are the phrenico-splenic ligament (often not mentioned in anatomy books), and the leino-renal which contains in between its two layers the pedicle of the spleen and the tail of the pancreas. The others, namely, the gastro-splenic, splenico-colic, and phrenico-colic ligaments are usually weak and inconstant in development. The latter is, however, considered by some authors as the chief support, acting as a hammock over which the lower pole of the spleen rests, so often called the sustentaculum leinis. Disturbance of this supporting mechanism will allow the spleen

to descend in its bed, and to acquire variable degrees of mobility in the abdominal cavity. Congenital factors, as absence of the supporting ligaments, a long mesentery, or a very narrow upper abdomen, account for some cases.[2] On the other hand, the majority of cases are due to acquired conditions, either increasing the weight of the spleen as in cases of splenomegaly, tumors or cysts; or reducing the intra-abdominal pressure, as after repeated pregnancies, or in visceroptosis.[12] The value of these several etiologic factors has been discussed by various authors, and more than one factor may be working in individual cases.

Clinically, the condition may be symptomless, and the spleen discovered accidentally in abnormal places in the abdominal cavity or pelvis. In some cases, especially if the organ is enlarged, dragging on the stomach or transverse colon interferes with their motility or blood supply, and so produces various gastric or intestinal symptoms. The majority of patients however seek surgical advice on account of the presence of associated complications. Axial rotation of the spleen may occur leading to torsion of its pedicle, which may be acute, chronic or recurrent.[2, 3, 4, 9, 31] In acute torsion the pedicle may twist many times, occlusion of the splenic vessels will result, and if the spleen is not removed hemorrhagic infarction of all or part of the organ will occur. A degenerative cyst may develop as a later complication. In severe cases the spleen will become gangrenous and if sepsis is superimposed a splenic abscess, localised or diffuse peritonitis will result. The included tail of the pancreas may slough with the spleen.[3] Associated acute intestinal obstruction may develop, in some cases due to inclusion of loops of small gut among the twists of the pedicle, in others due to adhesions and pressure of the twisted organ on the large gut; in still another group the spleen was already adherent to the pelvic colon, and when twist of the spleen occurred, a resultant volvulus of the pelvic colon developed.[2, 15, 28] Chronic or recurrent torsion will induce in the spleen a state of chronic venous congestion, leading to hypertrophy, perisplenic adhesions, or cyst formation. The spleen in its wandering may become fixed in abnormal places as the pelvis, right or left iliac fossae, there it may enlarge, become impacted, or press on the surrounding viscera, as the sigmoid colon, uterus or bladder, and there produce symptoms referred to them.[6, 28, 31]

The treatment of the condition is splenectomy, the old operations of splenopexy, or detorsion and splenopexy in cases of torsion have no place in modern surgical practice.

SUMMARY

A case of an enlarged spleen showing excessive mobility is reported, the enlargement is secondary to Bilharzial cirrhosis of the liver which was early and of the fine type. The condition was symptomless until the patient received a blow which caused a subcapsular rupture on the costal surface of the spleen, which later developed into a false blood cyst, and so, by adding to the weight of the spleen started to produce symptoms.

I wish to express my thanks to Prof. Abbas Hilmy for his kind advice and help, and for permission to publish this case.

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BOOK REVIEWS

"NEUROANATOMY," by Fred A. Mettler, M.D., St. Louis, C. V. Mosby Company, 2nd Edition, 1948. $10.00.

The 2nd Edition of this comprehensive textbook of neuroanatomy maintains the same general organization as the previous edition although some sections have been expanded, resulting in an increase to the text of 60 pages. The material has again been divided into two sections, the first dealing with gross aspects of the nervous system and the second with microscopic anatomy.

The section on the gross aspects of the central nervous system is only slightly modified from the previous excellent presentation of general relationships. New material has been added on the arterial supply and venous drainage of various portions of the neuraxis and the illustrations have been amplified. This section is largely descriptive and serves as a very valuable orientation of the macroscopic form of the central nervous system for all those dealing with this field. The excellent additions regarding the blood supply of the thalamus, basal ganglia and other structures are of great importance and the description of the relationship between the topography of the brain and that of the skull and extracranial structures continues to be valuable from the clinical viewpoint.

The second half of the book deals with the microscopic anatomy of the central nervous system, starting with the spinal cord and ending with the cerebral cortex. This material is profusely illustrated with drawings showing the main fiber tracts accompanied by a similar drawing showing the cell populations at that same level. This information is then summarized by various types of diagram which clarify the position and function of certain of the main tracts and association systems. The microscopic structure and function of the diencephalon are dealt with in great detail and this is supplemented by actual photomicrographs of sections of the thalamus which were not present in the previous edition. The relation between the various thalamic nuclei and the various areas of the cerebral cortex are also described in some detail, this being based on work which is not as yet complete. It might have been advantageous to summarize the known projections in text and diagram and omit some of this detail at the present time. Throughout this second section of the book, there has been a strong effort to try and correlate function and structure which serves to increase the usefulness of the material.

In spite of the detail with which the corpus striatum and diencephalon are described, both as regards form and what is known of function, the cerebral cortex is covered in a very scanty section with no mention of the large volume of recent work which correlates function of the various cortical areas with their structure both in man and the experimental animal. In addition, certain of the physiologic correlates of diencephalic structure and of the extrapyramidal system do not take into account a fairly large segment of recent work which would alter the emphasis which the author has placed on the quoted evidence.

This text continues to be one of the most complete in its field and, in spite of certain minor errors, represents an outstanding reference work. Because of the mass of intricate detail presented, however, its usefulness to clinicians is impaired.

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THE HOSPITAL CARE OF NEUROSURGICAL PATIENTS, 2nd Edition, by Wallace B. Hamby, M.D., F.A.C.S. Springfield, Ill., Charles C. Thomas, 1948. $3.00.

This little volume, which has recently come out as a second edition, should be a "must" on the reading list of all nurses engaged in the care of neurosurgical patients. There is also much in it of profit to the average interne and resident involved in pre- and postoperative neurosurgical care. The book is written in an easy, direct manner and,

while no attempt has been made to be complete to the last detail, all of the important points of pre- and postoperative care of neurosurgical patients are very adequately covered.

There is an especially good discussion on the relationships of the house officer to the patient, his relatives, and other members of the hospital staff, outside his immediate domain. It is noteworthy that the author points out that Cushing obtained necropsies in over 90 per cent of his cases and that one of the major duties of all concerned with the neurosurgical patient is the absolute necessity of obtaining necropsies.

The author starts with a relatively simple review of the fundamentals of gross neuroanatomy and proceeds to describe all the minor procedures in neurosurgery from venipuncture to ventriculogram. The paragraph on the technic and importance of cisternal puncture is particularly recommended. There is a very adequate discussion of the importance of arteriography and the means and methods of performing the Matas Test and carotid obliteration, before considering any type of ligation of the carotid. The author also elaborates on the use of catheters and the significance of good care of the genitourinary tract in neurosurgical patients, particularly those with spinal cord damage. Two relatively minor omissions were: first, the lack of discussion of the Penrose drain for adequately and simply controlling male micturition and second, the omission of the more modern method of the Munro set-up for tidal drainage, which obviates the use of much of the tubing and the old reservoir described by the author from the original Munro diagram of 1935. The discussion of the postoperative care of craniotomies and suboccipital craniectomies is particularly good in covering all the minute details so important to the young nurse and interne learning the "why's and wherefore's" of head dressings. A questionable omission is the use of gloves for *all* neurosurgical dressings, which we feel has cut down the incidence of infection to some extent at least. Although, in his introduction, Doctor Hamby stresses that he intends in no way to be specific concerning the use of antibiotics, the small section of one and three-quarter pages devoted to wound infection appears somewhat brief, especially when frequent laboratory studies, with cell counts and bacterial sensitivities, play such a prominent part in infection of the central nervous system. The frequency of lumbar puncture advised by Doctor Hamby is to be questioned somewhat and particularly its role in the immediate postoperative days following drainage of brain abscess. However, this is a matter to be decided only by the chief of the clinic and assumes different importance in various centers. The preoperative care of lobotomy is good, with much emphasis on the subsequent psychiatric care following operation while in the hospital. Again, the significance of frequent notes by the nursing staff and adequate psychotherapy are well stressed.

The size of this book and its readable print lend additional qualities to make it required reading for any group of students about to enter this specialized field. The book is completely indexed and the black and white illustrations by the author make all the procedures and anatomical points described readily understandable. We feel that Doctor Hamby has very ably accomplished that which he set out to do, namely, to supply a useful handbook which would be readily available on the floor nurse's desk for consultation by all house officers and nurses

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EDITORIAL ADDRESS

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